PEDIATRIC CLINICS OF NORTH AMERICA

610.5
P369
1955
May

COPYRIGHT, 1955, BY W. B. SAUNDERS COMPANY

COPYRIGHT UNDER THE INTERNATIONAL COPYRIGHT UNION

All Rights Reserved. This book is protected by copyright.
No part of it may be duplicated or reproduced
without written permission from the publisher.

MADE IN U.S.A. PRESS OF W. B. SAUNDERS COMPANY, PHILADELPHIA

Library of Congress Catalog Card Number: 54-6097

Medical
Taxon
5 6 55
34407

CONTRIBUTORS

MAY ISSUE

THOMAS G. BAFFES, M.D. Fellow in Surgical Research, and Staff Assistant Surgeon, Children's Memorial Hospital, Chicago.

JOHN A. BIGLER, M.D., F.A.A.P. Professor of Pediatrics and Head of Department, Northwestern University Medical School; Chief of Staff, Children's Memorial Hospital, Chicago.

ALFRED B. FALK, M.D. Attending Dermatologist and Departmental Head, Children's Memorial Hospital; Consultant in Dermatology, Louis A. Weiss Memorial Hospital, Chicago.

NATALIA S. FELIX, M.D. Research Fellow, Department of Pediatric Research, Michael Reese Hospital, Chicago.

SYDNEY S. GELLIS, M.D. Assistant Professor of Pediatrics, Harvard Medical School; Physician, Children's Medical Center; Pediatrician-in-Chief, Beth Israel Hospital, Boston.

JEROME GLASER, M.D., F.A.A.P. Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Pediatrician-in-Chief, Genesee Hospital, Rochester, N. Y.

TRYGVE GUNDERSEN, M.D. Professor of Ophthalmology, Boston University School of Medicine; Lecturer, Harvard Medical School; Surgeon, Massachusetts Eye and Ear Infirmary; Ophthalmologist, Children's Medical Center, Peter Bent Brigham Hospital and Massachusetts Memorial Hospitals, Boston.

L. MARTIN HARDY, M.D., F.A.A.P. Associate Professor of Pediatrics, Northwestern University Medical School; Medical Director, Children's Memorial Hospital Out Patient Department, Chicago.

LEE FORREST HILL, M.D., F.A.A.P. Chief of Pediatric Staff, Raymond Blank Memorial Hospital for Children, Des Moines, Iowa.

PAUL H. HOLINGER, M.D., F.A.C.P., F.A.C.S. Professor of Broncho-Esophagology, University of Illinois College of Medicine; Attending Broncho-esophagologist, St. Luke's and Children's Memorial Hospitals, and Research and Educational Hospitals; Consultant, Municipal Tuberculosis Sanitarium, Chicago, and U.S. Naval Hospital, Great Lakes, Illinois.

DAVID YI-YUNG HSIA, M.D. Instructor in Pediatrics, and Research Fellow in Bio-

logical Chemistry, Harvard Medical School; Assistant Physician, Children's Medical Center; Associate Physician, Beth Israel Hospital, Boston.

JOHN W. HUFFMAN, M.D. Associate Professor of Obstetrics and Gynecology, Northwestern University Medical School; Attending Gynecologist and Obstetrician, Passavant Memorial Hospital; Assistant Attending Pediatric Gynecologist, Children's Memorial Hospital, Chicago.

JAMES G. HUGHES, M.D., F.A.A.P. Professor of Pediatrics, University of Tennessee College of Medicine; Vice-President of Staff, Le Bonheur Children's Hospital; Pediatric Staff, John Gaston Children's Hospital, Memphis.

JOSEPH A. JOHNSTON, M.D., F.A.C.P. Pediatrician-in-Chief, Henry Ford Hospital, Detroit.

KENNETH C. JOHNSTON, M.D. Clinical Assistant Professor of Broncho-Esophagology, University of Illinois College of Medicine; Associate Attending Bronchologist, Children's Memorial Hospital; Attending Bronchoesophagologist, St. Luke's Hospital; Attending Bronchologist, Chicago State Tuberculosis Sanitarium, Chicago.

BENJAMIN M. KAGAN, M.D., F.A.C.P., F.A.A.P. Associate Professor of Pediatrics, Northwestern University Medical School; Chairman, Department of Pediatrics, and Director, Department of Pediatric Research, Michael Reese Hospital, Chicago.

HADDOW M. KEITH, M.D., F.A.C.P. Associate Professor of Pediatrics, Graduate School of Medicine, University of Minnesota Medical School; Staff, St. Mary's, Methodist, and Worrall Hospitals, Rochester, Minnesota.

KENNETH S. LANDAUER, M.D., F.A.A.P. Assistant Medical Director, The National Foundation for Infantile Paralysis, New York City.

HERMAN F. MEYER, M.D., F.A.C.P., F.A.A.P. Assistant Professor of Pediatrics, Northwestern University Medical School; Associate Attending Physician, Children's Memorial Hospital, Chicago.

ARTHUR HAWLEY PARMELEE, M.D., F.A.A.P. Clinical Professor of Pediatrics, University of Southern California School of Medicine; Senior Attending Physician, Children's Hospital, Los Angeles.

M. G. PETERMAN, M.D., F.A.A.P. Formerly Consultant in Pediatrics, Mayo Clinic, Rochester, Minnesota.

MILA PIERCE, M.D., F.A.A.P. Associate Professor of Pediatrics, University of Chicago Medical School; Staff, Bobs Roberts Hospital, Chicago.

WILLIS J. POTTS, M.D. Professor of Surgery, Northwestern University Medical School; Surgeon-in-Chief, Children's Memorial Hospital, Chicago.

JOHN LESTER REICHERT, M.D., F.A.A.P. Assistant Professor of Pediatrics, Northwestern University Medical School; Chairman, Department of Pediatrics, Chicago Wesley Memorial Hospital; Associate Attending Physician, Children's Memorial Hospital, Chicago.

MATTHEW M. STEINER, M.D., F.A.A.P. Associate in Pediatrics, Northwestern University Medical School; Associate Attending Physician, Children's Memorial Hospital; Consultant in Pediatrics, Grant Hospital, Chicago.

HART E. VAN RIPER, M.D., F.A.A.P. Medical Director, The National Foundation for Infantile Paralysis, New York City.

HARVEY WHITE, M.D. Assistant Professor of Radiology, Northwestern University Medical School; Attending Radiologist and Head of Department of Radiology, Children's Memorial Hospital, Chicago.

JUDITH L. WOOD, M.D. Assistant Attending Physician, Children's Memorial Hospital, Chicago.

CONTENTS

SYMPOSIUM ON DIAGNOSIS BY PRESENTING SYMPTOMS

Page 333	**John A. Bigler, M.D.**	*Foreword*
335	**Arthur Hawley Parmelee, M.D.**	*Examination of the Newborn Infant*
351	**Herman F. Meyer, M.D.**	*An Appraisal of Present Day Artificial Infant Feeding*
373	**Lee Forrest Hill, M.D.**	*Sudden Illness in Infancy*
391	**B. M. Kagan, M.D.** **Natalia S. Felix, M.D.**	*Edema in Infancy*
403	**Paul H. Holinger, M.D.** **Kenneth C. Johnston M.D.**	*The Infant with Respiratory Stridor*
413	**Jerome Glaser, M.D.**	*Frequent Colds in the Young Child*
427	**Mila Pierce, M.D.**	*The Pale Child*
441	**John A. Bigler, M.D.**	*Interpretation of Heart Murmurs*
449	**Sydney S. Gellis, M.D.** **David Yi-Yung Hsia, M.D.**	*Jaundice in Infancy*
465	**Judith L. Wood, M.D.** **L. Martin Hardy, M.D.** **Harvey White, M.D.**	*Chronic Vague Abdominal Pain in Children*

483 **James D. Hughes, M.D.** — *The Etiology of Vomiting in Infancy and Childhood*

503 **John A. Bigler M.D.** — *Diarrhea, Vomiting and Colic in the Young Infant Due to Milk Allergy*

513 **Thomas G. Baffes, M.D.** **Willis J. Potts, M.D.** — *Blood in the Stools of Infants and Children*

527 **John Lester Reichert, M.D.** — *Constipation in Infants and Young Children*

539 **John W. Huffman, M.D.** — *Menstrual Problems of the Adolescent*

553 **Matthew M. Steiner, M.D.** — *The Fat Child*

567 **Joseph A. Johnston, M.D.** — *The Thin Child*

575 **Matthew M. Steiner, M.D.** — *Enlargement of Breasts during Childhood*

595 **Haddow M. Keith, M.D.** — *Headache, Irritability and Fatigue*

605 **M. G. Peterman, M.D.** — *The Fainting Child*

615 **Alfred B. Falk, M.D.** — *Hemangioma in Infants*

625 **Trygve Gundersen, M.D.** — *Amblyopia ex Anopsia*

ANNUAL STATEMENT ON POLIOMYELITIS

629 **Hart Van Riper, M.D.** **Kenneth S. Landauer, M.D.** — *Poliomyelitis, 1955*

639 — *Cumulative Index*

FOREWORD

JOHN A. BIGLER, M.D.

This issue of the PEDIATRIC CLINICS OF NORTH AMERICA marks a deviation from the usual method of presenting pediatric clinical material. The approach has been through the use of *presenting symptoms* rather than specific diseases or organ pathology. It was felt that such a method should be tried because patients come to the physician with presenting symptoms, and actual clinical teaching uses the same approach.

It was also felt that such a method would bring out the individual authors' own approach to the specific problems the clinician is faced with when a parent brings an infant or child to him for advice. Of course, not all pediatric subjects lend themselves to this form of presentation without becoming too long or without the use of extensive outlines. The authors have been as comprehensive as they deemed necessary in handling the material to be covered from a clinical standpoint.

The subject matter selected for the individual authors is made up mostly of those problems that arise in a clinician's daily practice. Of the 22 articles included, about one third were written by physicians in full time positions and the remaining two thirds by clinicians in private practice. Only one of the articles is not specifically on presenting symptoms; it has to do with the prevention of blindness. Two others are general in scope: the selection of an infant's foods and the examination of the newborn infant. Both these latter are specific problems for which an infant is seen.

As Consulting Editor of this symposium I am extremely grateful to all the contributing authors.

EXAMINATION OF THE NEWBORN INFANT

ARTHUR HAWLEY PARMELEE, M.D.

The infant at birth has important adjustments to make in order to accommodate himself to a new environment. Some of these are vital and urgent; others are important, but can be made more leisurely without serious consequences.

This period of transition from intrauterine to extrauterine life is known as the neonatal or newborn period. It is properly set apart for special consideration because of the many unique anatomic and physiologic peculiarities which characterize it and because of the hazards to life in this period which are responsible for a high rate of morbidity and mortality. Its limits are not sharply defined. Statistically, it is the first month of life, but we are accustomed to think of it as the first two weeks, since by that time nearly all the important neonatal adjustments have been made. In a broad sense, however, it could be truthfully extended to include at least the first three months, since some of the influences of fetal life persist at least that long.

Most newborn infants make this transition successfully and, for the most part, with apparent ease. However, statistics show that approximately 20 infants out of every 1000 live births fail to survive the neonatal period, and this accounts for 60 per cent of the deaths in the entire first year. Furthermore, 83 per cent of these neonatal deaths occur in the first week, and of this 83 per cent, half occur in the first 24 hours. Only through better understanding of the peculiarities of the fetus and the newborn and the special hazards of this period can we continue our progress in reducing this high mortality rate. It will require also the combined and cooperative efforts of all who have a part in the welfare of the infant to bring this about.

Knowledge of the normal is the first step in recognizing variations from the normal. It is the purpose of this clinic to emphasize the neces-

sity of a careful examination and evaluation of each newly born infant and to point out normal characteristics. Certain deviations from normal will receive attention, but, for the most part, diseases of the newborn will only be mentioned in passing.

GENERAL CONSIDERATIONS

Appraisal of the health status of a newborn infant, just as in the older person, requires a knowledge of the history of the infant. And it must be remembered that he does have a past history, for he is not really "new," but only newly born. He has existed as an individual through a period of embryonic development and a period of fetal growth and in addition has had the more or less traumatic experiences coincident with birth. It is therefore important to have as much accurate information as can be obtained regarding the mother's health record during her pregnancy and regarding the circumstances of the birth itself. The kind of infant we have before us for examination will reflect the sum total of his genetic and environmental past and the minor or major insults to which he has been subjected.

Other considerations to be kept in mind will include the state of maturity reached at the time of birth as indicated by estimation of gestational age, birth weight and length and other manifestations of maturity. Also included must be a realization that maturation is a continuing function of growth, and even infants born at term are immature in the anatomic and functional development of many organs and tissues. Furthermore, it is important to keep in mind that for some time after birth there is a mixture of prenatal and postnatal physiologic peculiarities, and only gradually are the former completely replaced by the latter.

THE PHYSICAL EXAMINATION

Every newborn infant should have a careful and thorough physical examination as soon after birth as it can conveniently and adequately be done. The baby will have been inspected for gross signs of abnormality and the adequacy of its immediate neonatal responses noted in the delivery room at the time of birth. Unless otherwise indicated, the first detailed examination might well be delayed until a few hours later when many of the more vital adjustments have been made and a better evaluation is possible. A second complete examination is advisable shortly before the infant is taken home to check on the progress he is making and to make sure no new developments have occurred which you should be aware of and which might influence your report on the baby's condition to the parents and the instructions you give them. The findings

of each physical examination should be written on an appropriate examination sheet and be made a part of the hospital record of that infant.

General Inspection

General inspection of the infant as the first step in the examination will tell you much in a short time. You get immediately an impression of size, state of nutrition, probable state of maturity, presence or absence of cyanosis, of jaundice, of severe anemia, of respiratory difficulty, of distended or scaphoid abdomen; you note relative body proportions, posture, evidences of molding of the head and evidences of asymmetry of the face, chest or abdomen. All these are of significance and to the practiced eye of the experienced physician are of value in his final evaluation of the infant.

It is well, in making the physical examination, to delay the maneuvers which are likely to make the baby cry until you have completed the examination of the lungs, heart and abdomen; in other words, take advantage of periods of relative calm for those examinations which can be more adequately done when he is quiet. But for the purposes of this discussion the physical characteristics will not be discussed in relation to the order of the actual examination.

Posture

The newborn infant tends to retain, for some time after birth, a posture which reflects his recent intrauterine position. Since most infants are cephalic in presentation, what we commonly see is a generally flexed body, a short neck with the chin resting on the manubrium of the sternum, arms flexed at the elbow and internally rotated, hands fisted, legs somewhat flexed at the hips and knees and mildly bowed with the feet dorsiflexed. We call this "the posture of comfort," since attempts to forcefully change it as, for example, by straightening the arms or legs produce resistance and often crying. If presentation has been by face or brow, the head is usually extended in a position of opisthotonos and the neck appears long. The posture in breech presentations is usually quite characteristic: the legs are not bowed, but straight or even a bit knock-kneed, and in a frank breech presentation they are markedly abducted and externally rotated. Also the neck is elongated and the head extended.

Loss of neuromuscular tone will alter this characteristic posture or position of comfort. When there is extreme flaccidity of one or more parts, the cause should be sought for. This subject will be discussed later.

Body Proportions

The head and trunk present the appearance of a cylinder. The head, thorax and abdomen are round and of about the same circumference. The average full term infant has a head circumference of 34.5 cm. (13.5 inches), a chest circumference of 31.5 cm. (12.4 inches) and an abdominal circumference of about 31 cm. (12 inches).

The total length of the baby, or crown-heel length, is about 50 to 51 cm. (19.5 to 20 inches). The head and trunk make up about two thirds of this length and the legs one third, the crown-rump length (or sitting height) being 34 cm. (13.4 inches).

The average weight at birth is approximately 3300 gm. (7.26 pounds).

All these figures are slightly less for females than for males and for firstborn than for later born infants.

The Skin

The skin presents many interesting peculiarities and changes in appearance from day to day. At birth it is covered by vernix caseosa, but to an extremely variable degree. Often it is almost imperceptible and seen only in the axillary and inguinal areas and in the folds of the neck; usually there is none on the skin of premature infants. In some it is abundant and covers the entire skin surface. It disappears spontaneously within six to 12 hours after birth. The skin at birth has a soft and smooth texture which makes it extremely vulnerable to trauma and external irritants. The color is at first mildly pink with a bluish tinge, especially of the hands, feet and face. The hands and feet may remain mildly cyanotic for a day or two. Within six to eight hours the skin takes on a marked erythematous flush which gives it the so-called boiled lobster appearance. By the second day the flush is disappearing, the skin is lighter in color, and from then on some desquamation is evident. This may be only a mild flaky desquamation or may be in the nature of large scales or even sheets of cornified epidermis.

A high percentage of infants will show in the second or third day a varying number of small erythematous macules, often with a tiny whitish urticarial wheal in the center, scattered diffusely over the body. They look much like flea bites. This is called toxic erythema of the newborn. Its cause is obscure, but it is entirely benign and disappears spontaneously within a few days or a week. Also by the second or third day a great many babies, at least 50 per cent, will have an icteric discoloration of the skin due to physiologic icterus of the newborn. This too is a benign condition which disappears spontaneously within a week or two. It is important, however, to remember that icterus is also a symptom of more serious conditions, and these must be carefully differentiated. When icterus is present at birth or noted during the first 24

hours, it is almost certainly not physiologic and is probably due to erythroblastosis fetalis. Icterus that does not fade in the second week, but instead becomes progressively deeper, suggests obstructive icterus due to congenital atresia of the bile ducts, intrahepatic obstruction from inspissated bile due to blood group incompatability or other causes. Congenital viral hepatitis, congenital syphilis or sepsis may also need to be ruled out.

There is a tendency to edema in all newborn infants, and this is often manifest in the first days of life. The skin over the entire body frequently has a full appearance, and commonly there is a varying degree of pitting edema in the hands, feet and lower legs and at times over the pubis. Edema of the feet may persist for several days. By the second or third day the general edematous condition of the skin is gone and an interesting peculiarity can be demonstrated. This consists in a crinkly or crepe-paper-like appearance revealed when the tension of the skin is released. This is due to the loose attachment of the epidermis to the dermis, a condition peculiar to the newborn and to the aged. It is this anatomic peculiarity which accounts for the epidermolytic character of lesions seen commonly during the newborn period, i.e., impetigo, pemphigus, exfoliative dermatitis, and the like.

There is also a peculiarity of the subcutaneous fat which appears to be responsible for the occasional occurrence of isolated scleroderma-like indurated areas in the skin. These vary in size from that of a penny or smaller to that of a silver dollar or larger. They are round or oval, firm and sharply demarcated. When grasped with the fingers they feel like a button or a coin; they are firmly attached to the overlying skin, but freely movable over the underlying soft tissues. The surface often has a slightly purplish discoloration. They are known as areas of subcutaneous fat necrosis, probably due to trauma and to the chemical peculiarities of the subcutaneous fat. This fat is composed of a lower percentage of olein and a higher percentage of palmitin and stearin than that of the older child or adult, resulting in a high melting point, hence congealing with moderate reduction of local temperature. These indurated areas disappear spontaneously in a few weeks to a few months. They are commonly found at forceps pressure areas, often also on the back, buttocks and pectoral areas.

There is a fine downy growth of hair called lanugo which covers the body, but is more abundant over the shoulders and back. The amount and length of this hair vary greatly. It is almost imperceptible in some infants and very conspicuous in others, particularly in premature infants. It does not, however, constitute a sign of prematurity, since it is often quite as abundant in full term infants. Lanugo hair is shed within a few weeks.

Telangiectatic nevi are commonly found at the nape and often over

the glabella and forehead and also on the upper eyelids, the wings of the nose and the upper lip. These tend to become less and less conspicuous with increasing age.

Blue birth spots or mongolian spots are almost universally present over the sacrogluteal area in Negro, Mongolian and American Indian infants and commonly in Caucasians with a mixture of Mongolian, Indian or Negro blood and also occasionally in infants of supposedly pure Caucasian lineage. Specific pigment cells in the middle and deep portions of the corium are responsible for these spots, which are atavistic in origin. The spots become less and less conspicuous as the overlying epidermal pigment becomes more intense.

Often the skin, when exposed to cool atmosphere, has a dappled or marble-like appearance probably due to vasomotor changes in the cutaneous blood vessels.

The Head

The head, being the usual presenting part, seldom fails to show evidences of molding and some degree of what can justly be called physiologic trauma. Molding often causes the cranial bones to overlap at the sutures, and the amount of overlapping suggests something of the forces encountered in the passage of the head through the birth canal. This corrects itself rapidly and, if the infant is not examined until the second day, may be missed. In a rather large number of infants, especially of primiparous mothers, there is an asymmetrical appearance of the face due probably to an intrauterine posture in which the head was held in a fixed lateroflexed position so that the shoulder pressed into the neck and pushed the mandible toward the opposite side. This gives the face a lopsided appearance and usually produces some degree of malocclusion and also an obvious depression or fossa (shoulder impression) in the soft tissues of the neck. This and also the asymmetry and malocclusion disappear within a few weeks to a few months. This usually benign condition has some clinical importance because it is sometimes mistaken for facial nerve paralysis and also because on rare occasions actual facial paralysis does result from damage to the nerve by pressure of the shoulder on it as it emerges from the stylomastoid foramen.

Babies born by cesarean section before the onset of labor usually show no molding, and the head looks strikingly round. In breech presentations there is frequently a characteristic molding: it is flattened at the vertex, and the plane of the flatness slants upward and forward from the occiput. This may be the result of pressure of the fundus of the uterus against the flexed head.

The caput succedaneum is an example of true physiologic trauma to the area of the head that presents at the cervical os. When the bag of

waters ruptures, this area is subjected to greatly reduced pressure compared to the rest of the body, and this results in what can be likened to a vacuum cup action on it: the capillaries are overdistended, edema and petechial hemorrhages occur, and a congestive tumor is formed. It is seen on examination as a soft swelling with pitting edema and a bruised-looking scalp. It is not limited by the margins of a cranial bone. The tumor subsides within the first eight to 12 hours as a rule, but leaves evidence of its presence in the nature of petechiae or ecchymosis for a few days.

Another tumor of the head seen now and then is cephalhematoma. This is a subperiosteal hematoma that occurs usually on one parietal bone, though it may occur on both and on occasion is found on the occipital or frontal bone. It is not present at birth, but shows up only after a few hours, or may not appear until the second day. It is a fluctuant tumor varying in size from that of a walnut to that of an orange and always confined within the margins of a cranial bone. Within two or three days a distinctly raised bony margin can be felt at the limits of the tumor, giving the impression of a depressed fracture. This is due to the rapid development of new bone at the point of elevation of periosteum. Cephalhematomas require no treatment. They resolve spontaneously, usually within a few weeks, but always eventually, although in some instances they form an osteoma that may take a year or two to finally disappear.

The shape and size of the fontanels and the width of the sutures vary greatly. The average size of the anterior fontanel is about 2 by 2 cm. (¾ by ¾ inch) measured from the margin of one parietal bone to the opposite frontal bone margin, but the extremes are so great that no significance can be attached to it. This is also true of the width of the sutures. Hydrocephalus or microcephalus must be substantiated by evidence other than just the size of the fontanels and width of the sutures. There is one possible exception to this general statement, and that concerns the squamosal suture, the suture between the parietal bone and the temporal bone and greater wing of the sphenoid. This suture is usually barely palpable except in infants with hydrocephalus or macrocephalus, in which case it is significantly widened.

A rather large diamond-shaped parietal fontanel is sometimes felt as a widening of the sagittal suture a short distance anterior to the posterior fontanel. It is in the region of this parietal fontanel that one occasionally finds areas of thinness in the parietal bones that give under pressure like a ping-pong ball. This is called "physiologic craniotabes" (cranial osteoporosis) and is due to a mechanical factor of pressure plus a metabolic disturbance of bone formation. It disappears spontaneously. Spoon-shaped or troughlike depressions are seen in rare instances in the parietal and frontal bones, usually at or near the coronal suture. They

usually iron out of their own accord, but the deeper ones are sometimes elevated surgically.

The Eyes

These are difficult to examine. Attempts to forcefully separate the lids meet great resistance. This is true especially in the first few days of life, when the eyes are kept closed most of the time. By patiently waiting for the opportunity one can usually get a satisfactory view without resorting to force. Lifting the baby to an upright position will frequently cause him to open the eyes. Frequently one sees crescent-shaped subconjunctival hemorrhages at the margin of the cornea. Retinal hemorrhages occur in about 20 to 30 per cent of newborn infants according to some observers. There seems to be no residual trouble from these hemorrhages. The eyelids are often swollen and edematous, and there is some purulent discharge as the result of the prophylactic use of silver nitrate. An unusual or persisting purulent discharge demands bacteriologic study.

The Face

The face is frequently the site of numerous tiny whitish papules which are distended sebaceous glands or milia. They are particularly abundant over the nose and cheeks.

The lip margins show a sharp line of demarcation separating the skin portion from the mucous membrane; the skin portion constitutes only about one third of the visible lip surface. Over the central portion of the upper lip a superficial layer of cornified epithelium appears a few days after birth which later on is shed. This is called the "sucking callus." The gums frequently have conspicuously serrated margins on their alveolar ridges. In the roof of the mouth one usually finds small pearly white elevations near the median raphe at or just anterior to the junction of the hard and soft palates. These are epithelial inclusions and are called Epstein's pearls; they are shed after a few weeks. Occasionally these pearls are found also on the alveolar ridges. Commonly in the past, but now only on rare occasions, one will see an oval-shaped grayish membrane on either side of the median raphe of the hard palate just anterior to the soft palate. This is called Bednar's aphthae and is the result of abrasions of the mucous membrane caused by swabbing out the mouth with gauze.

To get a view of the oropharynx it is best to look while the infant is crying rather than use a tongue blade. It is almost impossible to depress the tongue of a newborn sufficiently to expose the pharynx. The mandible frequently appears underdeveloped, and the infant's chin recedes,

giving the appearance of true macrognathia, but not associated with macroglossia and not causing respiratory or feeding difficulty. This appearance is no longer noticeable after a few weeks. It is probably the result of pressure of the chin against the sternum in the flexed head position before birth.

The frenum of the upper lip may be quite pronounced and thick, extending to the alveolar ridge as a heavy cord where it is seen to be continuous with the median raphe of the maxilla. There is often a deep notch in the alveolar ridge at this point.

Underneath the tongue a frenulum is rather commonly seen, usually a thin veil-like structure which does not extend to the tip of the tongue, but it may be rather thick and extensive, so that when the tongue is protruded, a shallow notch is visible at its tip. This frenulum linguae does not seem to interfere with nursing, and it is certainly unwise to clip it at this age period.

The ear lobes vary greatly in shape and firmness, depending upon such factors as heredity, state of maturity and prenatal pressure. Premature infants have soft and often flat ear lobes because of lack of firm cartilage. Occasionally there is a fleshy preauricular tubercle or a preauricular sinus.

The Neck

Examination of the neck seldom reveals important findings. As previously stated, it is usually short in cephalic presentations except when the brow or face presents, and is likely to be thin and long in breech presentations. The folds of the neck are apt to be the site of mild skin irritation. Such abnormalities as a thyroglossal duct, a cystic hygroma and rarely a congenital goiter may be seen. The tumor of the sternocleidomastoid muscle caused probably by trauma, hemorrhage and fibrosis and known as hematoma of the sternocleidomastoid is not felt during the first week of life and seldom before the third week. It is a firm fibrous mass about olive-sized in the body of the muscle, and there may be some associated torticollis due to shortening of the muscle.

The clavicles should always be carefully palpated for evidence of fracture such as irregularity, angulation, pain and crepitus, since this bone is more frequently fractured during birth than any other, and there may have been little or no suspicion of its occurrence. Any indication of it should be confirmed by roentgenogram.

The Thorax

This is usually symmetrically cylindrical, but changes somewhat in shape with the full establishment of respiration. There are sometimes

peculiarities of shape such as flattening of the lateral aspects due to compression by the arms in utero, or to the presence of funnel chest or pigeon breast deformities. Occasionally an enlarged heart due to a congenital defect will cause a bulging of the thorax on the left. A definitely elevated and bulging sternum should cause suspicion of a pneumomediastinum, especially if there is associated dyspnea. There is often some retraction of the lower sternum in normal infants, but when marked and associated with retraction of the lower costal margins and suprasternal retraction, inspiratory difficulty is indicated. Practically all full term infants have engorgement of the breasts of some degree at birth, and after a few days there is lactation. This is never the case in truly premature infants.

The Lungs

The respiratory movements of the newborn are predominantly diaphragmatic with little visible participation of the intercostal muscles. Obvious strong intercostal activity suggests real respiratory difficulty. The breathing is usually irregular, often resembling Cheyne-Stokes breathing. The respiratory rate varies between wide extremes at different times in the same infant. Percussion, to be of any value, must be very light, since the chest wall is thin. Even then it is difficult to detect areas of pulmonary consolidations unless they are extensive, but with care the borders of cardiac dullness can usually be made out.

Auscultation requires patience and experience to get accurate information. Breathing may be so shallow that vesicular sounds can scarcely be heard, but if you wait long enough your patience will be rewarded by a succession of deep inspirations from which conclusions can be drawn. In the first day and frequently in the second or even the third day there may be a shower of fine crepitant rales at the end of deep inspirations in normal infants. Complete inflation of all areas of the lungs is accomplished gradually, and some areas of physiologic atelectasis persist for a while.

The Heart

The outline of the area of cardiac dullness can be made by careful percussion, but aside from determining whether or not it is in its proper position this is of little practical value. The size of the percussion area and its shape are variable, as is also the x-ray shadow of the heart in this age period, and defy evaluation. The overlying thymus is partly responsible for this. Auscultation needs to be carefully done with the infant quiet at the time, for respiratory sounds may be mistaken for murmurs, since respirations may be so rapid as to be synchronous with

the heart rate. A satisfactory method of keeping the infant quiet during this examination is to get him to suck on his fingers or on a pacifier.

Murmurs when heard also can be misleading. A murmur heard soon after birth may be gone the following day or soon after that; also there may be no murmur heard at first examination, but plainly heard a few days later. Under the stress of some pulmonary difficulty a murmur may be heard and disappear when the pulmonary condition has subsided. Other symptoms and signs must be taken into consideration before a diagnosis of a congenital heart defect is made.

The Abdomen

Inspection of the abdomen gives considerable information. It is usually rounded and full, but not distended. Normal muscle tone keeps it from bulging in the flanks. Diastasis of the recti muscles is a normal finding. The umbilicus varies in its structure: the skin portion may be long, in which case it is called umbilicus cutis, or the amniotic portion may encroach upon the skin of the abdomen, and then it is called umbilicus amnioticus. Neither of these variations is of importance. The appearance of the amniotic portion changes from day to day after birth as it becomes gangrenous and is finally shed. The stump should be carefully inspected for evidence of infection. A distended abdomen should receive attention, for it could mean a tumor, intestinal obstruction, a ruptured viscus or peritonitis. Palpation of the abdomen of a normal newborn is easy to do if the infant is not crying. The liver is readily palpated, usually 1 to 2 cm. below the right costal margin. The spleen is usually not palpable, but the tip of it is sometimes felt in normal infants. The left kidney can usually be readily palpated and also the lower pole of the right kidney. If the abdomen appears unusually flat or scaphoid, and especially if the lower thorax appears widened (a turnip-shaped abdomen), one should suspect a diaphragmatic hernia.

The Genitalia

The genitalia of both male and female infants vary considerably in appearance. In the male there is great variation in the size of the scrotum, but less in the size of the penis. Both testicles are usually in the scrotum, or one or both may be felt in the canal, from whence they may or may not be easily forced into the scrotum. True cryptorchism is relatively rare, and one should hesitate about making this diagnosis until after repeated examinations under good conditions of relaxation. Edema of the scrotum is common. Hydrocele also is frequently seen; usually it is transitory, but may persist for several weeks or months. A true hernia is rarely seen in the newborn period. It is more likely to occur in a pre-

mature infant. Physiologic phimosis is the rule in newborn males, but in some the foreskin may be retracted sufficiently to reveal the urethral meatus, and in a few the foreskin does not cover the tip of the glans penis. A hooded prepuce in which the dorsum of the glans is covered but the ventral surface is bare is almost always associated with hypospadias of some degree.

In the female there is as much variation in the development of the labia majora as there is in the scrotum of the male. They may be full and bulbous and cover the relatively large labia minora and clitoris or poorly developed, leaving the prominent clitoris and labia minora bare, which is the case in nearly half of the full term infants and in all premature females. There is a viscid mucoid discharge from the vagina in all full term females, but not in prematures. In a fair percentage the discharge may be blood-tinged or frankly bloody, a response to prenatal hormonal influences. A pinkish, fleshy hymenal tag is usually seen protruding from the floor of the introitus.

In breech delivery the appearance of the genitalia and perineum is greatly altered by edema and bruising.

The Anus

The anus should be inspected and the history of the passage of meconium ascertained. Routine rectal examination in the neonatal period is, in my opinion, superfluous and, because it is traumatic, unwise. It should, however, be done if there is any question about the free passage of meconium.

At the end of the coccyx one frequently finds a dimple. This common coccygeal dimple or sinus is probably due to maldevelopment of the caudal ligament and causes no trouble. There is probably, however, some developmental relationship between it and the rare pilonidal sinuses which are remnants of the caudal end of the medullary canal.

The Extremities

Birth trauma may cause injury to the brachial plexus, in which case the arm assumes a typical position of extension, adduction, internal rotation and pronation. Traumatic separation of the proximal epiphysis of the humerus may produce a somewhat similar position of the arm, but this is a pseudoparalysis similar to that caused by syphilitic separation of the epiphysis. Rarely the legs may be limp and flaccid from injury to the spinal cord. Fractures and dislocations are seen on rare occasions. Congenital dislocation of the hip is seldom diagnosed with certainty in the newborn period. Intrauterine posture is responsible for several peculiarities of the feet. In nearly every newborn the feet are

markedly dorsiflexed, and the dorsum of the foot can be made to lie against the anterior aspect of the tibia without effort. This is pes calcaneus or talipes calcaneus. It corrects itself later. There is often rather marked pronation of one or both feet. This also corrects itself, but may persist until walking is well under way. A metatarsalis varus deformity is fairly common, and need give one no concern when the metatarsals can readily be brought into line by passive manipulations. Parents can be instructed to carry out these manipulations, and there is little likelihood of any residual deformity.

Evaluation of Neuromuscular Status

The development of the nervous system at the time of birth is still in its early stages; consequently the neuromuscular behavior has distinct peculiarities. In a sense the infant is still largely a spinal animal and functions at a subcortical level. For example, he will often present a tonic neck reflex posture similar to a sign of decerebrate rigidity, his head turned to one side and the arm and leg on that side extended while the opposite extremities are flexed. Also he has a startle reflex (Moro reflex). When he is lying prone, if the table on which he is lying is struck sharply with the fists or if his head is flexed and then quickly dropped backward, producing a mild lordosis, he will extend his arms, spread his fingers and bring his arms forward in an embracing movement. This is a test that should never be omitted, since an abnormal response is significant. An absent or incompletely performed reflex signifies cerebral damage of some sort. A unilateral response usually means a fractured clavicle, brachial plexus injury or separation of the proximal epiphysis of the humerus on the side that fails to respond normally. The infant will suck on anything that touches his lips; he will firmly grasp your finger if it is put in the palm of his hand, and will likewise grasp it with his toes when it is pressed against the ball of his foot. A positive Babinski sign is obtained in the newborn, also a masseter reflex when the chin is tapped. Frequently a facial phenomenon (Chvostek sign) is present. Striking the patellar tendon often produces a mass reflex in which there is a leg jerk instead of just a knee kick. If held up on his feet, he will make alternate walking movements. Often one sees coarse tremors of the arms and legs and chin. True sustained ankle clonus is not normal in the newborn and when present denotes cerebral pathology.

Other Characteristics

The Urine. Urine is usually passed soon after birth, but may be unnoticed. Not infrequently passage of urine may not be noted for as long

as 24 or even 48 hours, and sometimes even then only a small amount may be passed. This is not necessarily abnormal and need not cause concern. The kidneys are immature in their functional capacity. The urine is of low specific gravity. It frequently contains albumin and may contain red and white blood cells; it also contains a high concentration of urates and uric acid. The diapers frequently show a pink or salmon-colored stain because of this. Such urine is known as infarct urine.

The Stools. The first stools are meconium stools, a tenacious, blackish material. Meconium is often passed soon after birth. The first meconium stool is seldom delayed longer than 12 hours. By the third day the stool has lost most of its meconium characteristics and becomes lighter in color and contains some food residue and mucus. This is the transitional stool.

The Blood. In the first week the blood is characterized by a high erythrocyte count (5,800,000), a high hemoglobin level (18 gm.), a relatively high leukocyte count (20,000 in the first two days, falling to 10,000 to 12,000 by the end of the first week) and a normal platelet count. At birth the polymorphonuclear cells constitute about 70 per cent of the total white cells and continue to predominate until the fifth day, after which the lymphocytes predominate.

THE PREMATURE INFANT

The premature infant deserves special attention which, because of lack of space, cannot be given in this discussion. Suffice it to say that the prematurely born infant has the same adjustments to make as does the full term infant, but is handicapped by an immaturity of development of his organs and tissues. A certain stage of maturation is necessary for survival in an extrauterine environment, and his chances of successfully making the essential neonatal adjustments are in a large measure in direct proportion to his gestational age, that is, the stage of maturation reached at the time of birth. This is not to say that the events of his birth and the kind of care he gets after birth are unimportant; these are, in fact, of the greatest importance. It is only to emphasize how essential it is that we learn to evaluate each one on the basis of his probable gestational age and not be content to lump all infants weighing 2500 gm. or less in one group as prematures without further analysis.

SUMMARY

A method of procedure in examining the newborn infant has been outlined with special emphasis on normal characteristics and variations that fall within normal limits. Examination of the normal newborn increases in interest as we gain more understanding of the anatomic and

physiologic peculiarities of this period of transition from fetal to postnatal life.

REFERENCES

1. Barnett, H. L.: Kidney Function in Young Infants. Pediatrics, 5:171, 1950.
2. Baumgartner, L., Pessin, V., Wegman, M. E., and Parker, S. L.: Weight in Fetal and Newborn Mortality. Pediatrics, 6:329, 1950.
3. Dunham, E. C.: Premature Infants. A Manual for Physicians. Children's Bureau Publication No. 325. Washington, D.C., U.S. Government Printing Office, 1948.
4. Howard, P. J., and Bauer, A. B.: Irregularities of Breathing in the Newborn Period. Am. J. Dis. Child., 77:592, 1949.
5. Howard, P. J., and Bauer, A. B.: Respiration of the Newborn Infant. Am. J. Dis. Child., 79:611, 1950.
6. Parmelee, A. H.: Molding Due to Intra-uterine Posture. Am. J. Dis. Child., 42:1155, 1931.
7. Parmelee, A. H.: Skin Conditions in the Newborn. M. Clin. North America, 30:17, 1946.
8. Parmelee, A. H.: Physical and Physiologic Signs of Prematurity. Ann. West. Med. & Surg., 2:71, 1948.
9. Parmelee, A. H.: Hormonal Inadequacies in the Premature Infant. Abraham Levinson Anniversary Volume, Studies in Pediatrics and Medical History. New York, Froben Press, Inc., 1949, pp. 215–220.
10. Parmelee, A. H.: Management of the Newborn. Chicago, Year Book Publishers, Inc., 1952.
11. Parmelee, A. H.: The Joint Responsibility of Obstetrics and Pediatrics in the Problems of the Newborn. Wisconsin M. J., 41:582, 1942.
12. Reardon, H., Wilson, J. L., and Graham, B.: Physiological Variations of the Premature Infant. Am. J. Dis. Child., 81:99, 1951.
13. Salmon, G. W., Forbes, G. B., and Davenport, H.: Airblock in the Newborn Infant. J. Pediat., 30:260, 1947.
14. Sanford, H. N.: Care of the Skin of the Newborn Infant. J. Pediat., 2:68, 1937.
15. Sanford, H. N., and Grulee, C. G.: The Newborn, in McQuarrie, I., ed.: Brennemann's Practice of Pediatrics. Hagerstown, Md., W. F. Pryor Company, Inc., 1945, Vol. 1, Chap. 42.
16. Scott, R. B., and Wooding, C. H., Jr.: Congenital Aural Fistula. J. Pediat., 36: 784, 1950.
17. Smith, C. A.: The Valley of the Shadow of Birth. Am. J. Dis. Child., 82:171, 1951.
18. Smith, C. A.: The Physiology of the Newborn Infant. Springfield, Ill., Charles C Thomas, 1945.
19. Weiner, L. R., and Richmond, J. B.: The Diagnosis of Surgical Conditions of the Newborn Infant. J. Pediat., 36:107, 1950.

4614 Sunset Boulevard
Los Angeles 27, California

AN APPRAISAL OF PRESENT DAY ARTIFICIAL INFANT FEEDING

HERMAN F. MEYER, M.D.

The justification for including so mundane and elementary a subject as *infant feeding* in this symposium is twofold. Primarily, the subject matter in this field from time to time needs to be reviewed, appraised and epitomized to insure its usefulness. Otherwise the perspective of accumulated data loses focus in the haze of opinion and products which are available in profusion. Secondly, a situation presently exists which is an evolutionary end product of old and modern teaching of infant feeding. There are those who cling to the concept that this subject is almost an exact science, and so treat their prescribing of infant foods to the babies under their care and impart the same didactic dogma to those who come into their writing and teaching spheres. The other school of thought is that commonly expressed by the "feed-them-anything" dictum, which has many modern proponents. An effort will be made to bridge these two extreme views and to orient the reader in the present status of confusion as to the teaching precepts in this special field of pediatrics. An amplification of the simple chemical and physiologic rules involved in milk digestion generally accepted by modern nutritionists will be presented. An effort will be made to classify the multitudinous products of both fresh and proprietary milk foods available for practical use to the physician in his feeding practice.

Because of the singular content of the material of this paper, Dr. John A. Bigler directed that this contribution be presented in an outline and expository style rather than in the format of the other papers in this symposium. Diagnosis by Presenting Symptoms would not pertain to an exposition of infant feeding. The Editor also advised that the discussion be limited within the confines of artificial feeding of infants. To include the important subject of breast feeding would perforce extend the discussion to impractical proportions in this limited endeavor.

HISTORICAL SETTING

Since the beginning of Man's struggle for existence, the pre-eminent need for an adequate food for his suckling young was probably second only to *self*-preservation. From archeological discoveries, by frequent allusions in the records of Man's writings and inscriptions, and from the interpretation of his art forms from the beginning of prehistoric time—from these sources we know that Man's quest included this search for adequate nutrition for his young.

Earlier Endeavors

Artificial feeding as an art or science is a matter of recent times. Only in the last five or six decades can one even speak of a *science* of artificial infant feeding. Among the Ancients, anything other than breast feeding in this sense was unknown if we may judge by the records handed down to us. In vain does one look for a reference to the subject in Hippocrates, Galen or the Arabians, or from any other ancient physicians or philosophers. Only crudely empiric efforts were made throughout the Middle Ages and, even up to less than a century ago, led to futile and even grim results with young and older infants.

The earliest attempts at artificial feeding consisted in making the goal of all effort that of adapting the milk of a foreign species to the human infant. Many different mammals were used for this purpose, including the goat, ass, camel, llama, caribou, dog, horse, reindeer, water buffalo, sheep and, of course, universally the cow. Each reflects the race or civilization extant at the time of its use, and also implies the era or country which employed it. The feeding of the infant was arranged either by direct nursing from the udder by the baby, or by indirect feeding from a vessel after the milk had been drawn. The use of such milks is still basic and forms the starting point of nearly all artificial feeding.

The results that followed the use of unaltered whole milk from any mammal were so disastrous that dilution with water naturally followed as a simple method of making milk "weaker" and more acceptable to the infant gastrointestinal tract. Later, sugar and other carbohydrates were added to equalize the loss in caloric content due to dilution, a principle which is still fundamental. The advent of bacteriology, a newer knowledge of the chemical and physical behavior of human and other milk, the discovery of vitamins and their significance in nutrition—all were further milestones of great importance in the evolution of modern infant feeding.

Recent Achievements

The modern epoch of scientific infant feeding began some 60 years ago with Biedert in Germany and Rotch in this country. Steadily in-

creasing progress has been made since that time, and in the last three or four decades it has been placed on a scientific basis as firmly as any other branch of medicine. As happens in such widely diversified endeavors by many outstanding investigators of the time, there was an ever-increasing confusion of ideas, theories and practices, which in retrospect seems almost ludicrous in the light of present knowledge. We no longer evolve infant feeding formulas with slide rules and higher mathematics. Today we have emerged from a "chaos of complexity" into what we might call a "chaos of simplicity."[2] We are actually confronted in any given case by the question of which simple method of feeding to choose from in a large and constantly increasing assortment that all lead to the same result, differing only in substance rather than in principle.

Mention must be made of the final chapter in this devious and interesting history of infant feeding. It was Drs. Joseph Brennemann and McKim Marriott of this country who set the stage for the finale in this drama of confusion. Beginning with Brennemann's observations in 1910 on the curd of cow's milk in vivo, pragmatism was created out of chemical disorder. Utilizing all the information available on the digestion of casein in the infant stomach, he contributed toward clarifying the perplexity which reigned between the various feuding schools of thought. After similar observations had been made on curd formation by Marriott, in which he extolled the importance of the *hydrogen ion* in the gastric digestion of casein, the main obstacles in the chemistry and physiology of infant feeding appeared to have been determined.

An air of finality seems to have been cast on this controversy by the Council on Foods of the American Medical Association, which adjudicated this minor dispute in a report,[5] part of which is here quoted: "Brennemann, who as a result of his former experiments interpreted the value of acid milks in terms of curd texture, undertook a crucial experiment to evaluate the role of the acid. . . . [He] was forced to the conclusion that curd texture, and not acidity, is of prime importance and that the value of acid milks lies in the modification of the curd. This conclusion has been amply supported by the work of Lynch, and of Jeans and Stearns."

In recapitulation, it may be said that the more important phases of this history transpired recently and in the period of most of our lifetimes. The accomplishment of this feat is unique in that this magnificent achievement was paced by the strides of biochemistry of this period, and in a somewhat smaller sphere in the accompanying advancement of the general standard of living in this country. It may come as a relief to those who think they have not kept up with the current literature and practice of infant feeding to learn that *no fundamental changes* have been made in our knowledge in this field since 1935. It is also interesting to observe that after centuries of elusive

search for some substitute as a suitable food for his newborn young, this mammal known as Man solved the problem effectively and in a brief span of time.

ESSENTIAL CHEMICAL AND PHYSIOLOGIC PRINCIPLES*

Types of Feeding

The use of cow's milk in this country forms the basis for practically all artificial infant feeding. Simple dilution of this milk with water and usually the addition of a carbohydrate, is still the fundamental and the simplest method of procedure. It differs from *percentage feeding*, which had its vogue at an earlier day, in its greater simplicity, dealing with *amounts* of milk, sugar and water rather than *percentages* of the differ-

TABLE 1. *Approximate Percentage Composition of Milks*[2]

	FAT	CHO	PROTEIN	MINERALS
Human	3.5	7.5	1.25	0.25
Cow	3.5	4.7	3.4	0.75
Goat	4.0	4.5	3.5	0.93

ent milk-mixture elements (fat, carbohydrate, protein, minerals). In the main, by the *simple milk dilution feeding* method, these elements are reduced by dilution. The carbohydrate, which is 7 per cent in human milk, must be added back to a nearer "normal" amount to satisfy fuel requirements. (This statement may be questioned by certain investigators—see Milk Mixtures without Added Carbohydrate.)

The degree of dilution necessary to make cow's milk more acceptable to infant digestion is arrived at arbitrarily, varying with the state of the protein in the milk—whether boiled, alkalinized, acidified or enzymized. The degree of dilution also depends upon the practical experience of the physician. It finally depends on the infant himself whose progress in weight-gaining, evidence of satisfactory milk digestion, and personal receptiveness to the preferred combination are the final indices of any successful milk formula.

A variant to the *simple milk dilution method* was introduced some 20 years ago which emphasized the value of the milk mixture in terms of caloric units, and this was known as *caloric feeding*. It was simply an evaluation of any calculated formula by computing the caloric values of the various constituents, and deciding whether the total calorie intake was compatible with an expected increment of weight-gain. The method

* Only conventionally accepted basic essentials will be quoted here. The limitations of this paper do not warrant elaboration of the known chemical and physiologic facts. The more interested reader will find an amplification of these principles and the scientific authority for them by referring to the texts on this subject: Jeans and Marriott,[11] and Meyer.[14]

served as an adjunct rather than a severe requirement. The average experienced physician rarely pauses to compute calories. Here again the specific nutritional state of the infant directs his course, and he is prone to exceed rather than to minimize the calorie intake. If an infant fails to gain weight on what seems to be an adequate offering, this computation of calorie calculation is indicated. To compute or prescribe a milk mixture with only the strict calorie requirements in mind (50 to 55 calories per pound of body weight), without noting the effect or needs of the infant, again illustrates the fallacy of dogmatism in formula prescribing.

Basic Nutritional Requirements

In the computation of an infant milk mixture, certain essential nutritional needs must be fulfilled, and these have been more or less arbitrarily agreed upon by infant nutritionists. They are here presented in an abbreviated form, and the reader is urged to seek in quoted references for the origin and scientific authority of these specific requirements.[11, 14]

1. *Proteins.* One and one-half ounces of cow's milk per pound of body weight equals 1.5 gm. of protein per pound, which equals one tenth of body weight. An excess of protein is well tolerated.

2. *Carbohydrates.* One-tenth ounce per pound of body weight equals 1 ounce per 10 ounces of milk prescribed, which also equals 1 per cent of the body weight. One third of the carbohydrate should be derived from the milk of the mixture, and the remainder added in the form of starch or sugar. Later in the first year the carbohydrate is given in the form of a starch cereal, and the carbohydrate in the milk formula may be reduced at that time.

3. *Fats.* Anywhere from 3 to 5 per cent is included, no specific amount being stipulated. If the fats are restricted, a larger amount of protein or sugar, or both, is required for energy sources. The suitable quantity of fat is supplied in amounts of milk which furnish the required amounts of protein. An excess of fat is not to be desired.

4. *Minerals.* An adequate mineral-salt intake is supplied to any infant when 1½ ounces of milk per pound of body weight are given. Enough iron is stored in the liver of the normal infant (from the hemoglobin breakdown after birth) to suffice until about the fourth or fifth month. This deficiency is then usually made up by the addition of the solid food supplements (egg yolk, fortified cereals, vegetables and fruit) which are usually added before this time, except in the completely milk-fed infant who refuses or is not offered these iron-containing foods in the first year.

5. *Water.* The requirement for water varies from 10 to 15 per cent of the body weight, or may be expressed as 1½ to 2½ ounces per pound of body weight. This is supplied in the milk itself, in the diluent of the milk mixture, and supplemented to instinctive demands by offerings of water and fruit juices between feedings.

6. *Calories.* The average requirement for growth in the first year is 50 calories per pound of *expected* weight, two thirds of this caloric need being supplied by the milk and one third by the added carbohydrate.

7. *Vitamins.* Any *normal* infant ingesting 18 ounces of cow's milk, or a comparable amount in a proprietary milk food, or its equivalent of human milk (24 ounces), receives all the vitamin A and all the vitamin B fractions (including vitamin B_{12}) needed for optimum growth. There is a deficiency of vitamins C and D in both human and cow's milks, and these should be supplemented as early as possible in the first month of life. Thirty to 50 mg. of vitamin C, and *no more* than 400 I.U. of vitamin D, should be administered daily in any acceptable form.

Unnecessary and excessive vitamin prescribing and ingestion are to be deprecated. Infants given a daily dose of 2000 I.U. of vitamin D achieve less growth than infants

receiving 135 I.U., and far less than those given 400 I.U.[8,17] In careful studies on premature infants it has been concluded that there appeared to be no difference in efficacy in the various types of commercially available vitamin D preparations in preventing rickets or promoting growth.[8]

Importance of Gastric Digestion of Protein

As stated previously, the fundamental emphasis of the digestibility of milk (a soft curd) has been established, and remains the essential criterion of the acceptability of any milk by the infant stomach. It had long been known that various agents, added empirically to cow's milk, seemed to facilitate and accelerate the digestion of any milk mixture. We now know the exact reason for this. The need for producing a softer curd texture was the important scientific factor which explained these clinical observations made by earlier practitioners. Some of these

TABLE 2. *Ratio of Components in Gastric Digestion of 2 Milks*[2] *(Comparison of Innate Digestibility of Human and Cow's Milk in the Initial Digestive Effort in the Stomach)*

	LACTALBUMIN (*Whey*)	CASEIN CURD (*Calcium Caseinate*)
Human milk	60%	40%
Cow's milk (raw)	15%	85%

casein modifiers are still in use, local customs and provincial practices exemplifying the value of their uses which were rudiments of nutritional truths later uncovered.

A list of these agents and procedures is interesting enough to mention here: lime water, milk of magnesia, sodium citrate, cereal waters, cream mixtures, cow's milk whey, buttermilk (acid), peptones, enzymes (*chymogen, pegnin* and *rennin*), dilution with water, acidifying (addition of lemon juice, orange juice, vinegar, hydrochloric, citric, acetic or lactic acids), boiling, drying and evaporating. That these additives and procedures rendered a useful service cannot be doubted. They all contributed to the end result of better digestion of milk by implication, in simple clinical usage. All but the last six have fallen into disuse, because almost all milk is now boiled, evaporated, dried, acidified or enzyme-predigested. Each process achieves a soft curd texture in the infant stomach more efficiently than the empirical methods of an earlier time. This faculty of softness of the calcium caseinate curd is the criterion of the digestibility of a given milk, and is known as the *curd tension.*

Curd Tension

It was logical that so important a principle as curd softness should have a method whereby this characteristic could be measured. To say

that the curds of one milk are *less tough*, are *softer* or *more flocculent*, or *smaller* or *larger* than those of another is not definite enough for comparison. To be able to state by some *quantitative* term how one milk varies from another in this characteristic is another standard of rating milks. Many ingenious and inventive techniques have been devised to study the tensile strength of the calcium caseinate curd in vitro.

Briefly, most of the methods designed to measure curd tension consist in coagulating the milk to be studied in a vessel by a solution of *rennin* and *calcium chloride*. The force required to pull or push a horizontal knife blade of specified weight and size through this coagulum is measured on a spring balance. This resistance is indicated in terms of grams of force under standard conditions, and the *curd tension* is measured in *numbers of grams*.[4] The ideal score of any milk is a curd tension of *zero* ("0"). Satisfactory curd tension implying good digestion is any milk having less than *20 gm.*, although some investigators allow an upper limit of *33 gm.* Human and evaporated milks are examples of milks which have a *"0" curd tension*, and many proprietary food manufacturers qualify their products in the "0" range, and so state in the descriptions of their preparations.[14] This provides still another criterion for the evaluation of fresh and proprietary milk foods available for infant consumption.

FRESH AND PROPRIETARY INFANT MILK FOODS

Most beginners and veterans in the practice of infant feeding are mystified and perplexed by the multiplicity of infant foods available for use. Professional journals carry acceptable advertising extolling these foods; manufacturers' representatives courteously interview the busy physician, portraying reputable houses and exhibiting creditable scientific claims; the mail daily contains multiple reminders of the many preparations addressed to the puzzled doctor as to the advantages of one food product over another. Little wonder is it that the bewilderment of the physician becomes greater and his incredulity mounts against further inroads on his intelligence and specific information in this field.

Much of the difficulty and uncertainty arises from the fact that there is extensive duplication in the preparation of baby milk foods by various manufacturers, illustrated by the fact that 42 companies produce over 460 brands of evaporated milk; that nine companies prepare 23 different liquid and dry premodified mixtures; that eight make 16 hypoallergenic preparations; and 16 offer 27 carbohydrate additions and modifiers. Many of the products vary in their methods of manufacture and differ only in minor points of chemistry, but are designed essentially for the same purposes within a class. They exemplify known principles or functions and are, therefore, much the same. It is stating the

obvious to say that *there are too many preparations available to serve the same requirements* and that *no infant gut can discriminate between the finer variations within the same group of products.*

This plethora of milk foods does not imply that any of them are not worthy of their functions. There is no evidence that physicians are de-

Fig. 1. The modern version of "a doctor's dilemma," or, the physician's armamentarium for artificial infant feeding.

ceived, that the parent-infant consumers are exploited, or that any false claims are made by the manufacturers. Each of the foods represents at least one or more of the nutritional principles elicited from the literature or obtained by private research, albeit minor differences are at times amplified by some of the proprietary houses in the zeal of competitive selling and promotion.

A CLASSIFICATION OF INFANT MILK FOODS

When all the 76 fresh and proprietary milk products and the 27 carbohydrate additives available in America are assembled, and when their

contents, intended functions and clinical uses are examined, some clarity can be discerned and a classification may be suggested. This arrangement is an arbitrary one, and others may be made which would also fulfill the needs of orientation. This one is suggested merely to facilitate the understanding of the physician and to help create some organization in this apparent chaos.

In the following pages the milks are divided into nine groups, each of these divisions is defined, and the specific foods of these groups are mentioned by name. Space would not permit listing the manufacturer of each, the chemical content, the clinical uses, and how formulated. These data may be found elsewhere.[14]

Group I: Fresh Milks

Whole Pasteurized Milk and *Homogenized Vitamin D Milk* (diluted and with a carbohydrate added) long have been used in infant feeding as basic mixtures. They are well tolerated by most infants, are inexpensive, and are almost universally available. Steaming for three minutes in the double boiler at the boiling point should be a requirement to facilitate curd softening. The homogenizing of the fat hastens the emptying time in the stomach and increases the action of the *lipase* on the smaller globules in intestinal digestion.

Sof Kurd Milk is an example of curd reduction of milk by the alkali-exchange method. It may be used formulated as regular milk for the young infant, or it may provide a transition from any formula mixture to whole milk in the older baby.

Enzylac Milk represents a milk with an enzyme added (mostly *trypsin*) previous to pasteurization, producing a softer curd for infant digestion. Some proteolytic changes are also affected in the protein molecule, which is said to aid in the intestinal digestion of milk. This milk may be diluted with a carbohydrate added, or used as produced. Obviously this milk does not need to be boiled for sterilization because of its inherent low cell count and its previous enzyme treatment of curd softening. It is available in a fat-free (0.1 per cent) product when a skimmed milk is indicated. A convenient service is also available for transient infants by the use of tablets containing the enzyme, which, when added to whole milk under the proper conditions, produces Enzylac Milk for use in the home.

Certified Milk had its halycon days when the cell counts of unclean milks were high, and it represented one method of assuring clean whole milk unchanged by boiling. Its uses are limited in the present era of almost sterile, fresh commercial products, and it has the disadvantage in infant digestion of having a high curd tension if used as produced.

Goat's Milk, usually Certified, is used primarily as a fresh milk prod-

uct of another species when there is a proved sensitization to the lactalbumin fraction of cow's milk in allergic states. It is formulated as is cow's milk by dilution, possibly boiling if not Certified, and by carbohydrate additives.

Skimmed or *Fat-Free Milk* (0.2 per cent fat) may be had in the fresh state, and is used when a lowered fat intake is indicated. Because the vitamin A is contained in the removed fat fraction, adequate doses of vitamin A are added back in most fresh, dairy, skimmed milk products.

High Fat Milk is also known by specific commercially given names as *Guernsey, Extra-Rich,* and so on, and may be used when a higher fat content is desired and there is no demonstrable intolerance. It contains 4.5 per cent fat, which is about 1 per cent more than regular milk products (3.4 per cent). Its uses in infant feeding are limited.

Buttermilk, either cultured or artificially produced (acidified), is antiquated by the newer and more easily controlled lactic acid-added cow's milk mixtures, or the powdered proprietary lactic acid milks available.

Acidophilus milks are vestiges of that academic and still disputed effort to produce an acid flora in the infant intestinal tract instead of a putrefactive or gas-producing culture of the *colon-aerogenes* group. These milks are known by various proprietary names—*B. Acidophilus, Bac-T, B. Bulgarus* and others—not all identical, but varying as to organism and method of production within the limits of this classification. These milks are indicated in that ill defined and controversial territory surrounded by many hypotheses and conflicts of pedantic opinion and clinical research, overhung with an aura of food faddism. The fact that the breast-fed baby "enjoys" an acid intestinal flora[15] carries little other than academic weight that such a state is necessary for satisfactory digestion of milk.

Med-o-Milk is *canned* whole, *fluid, fresh* milk, processed by sterilization, pasteurization and homogenization, during which time the milk is never exposed to the air from the time it leaves the cow until the moment the can is opened by the consumer. The milk is said to stay "sweet and fresh tasting" for eight to 12 months after canning; the curd tension is lower than that of whole milk because of the heat treatment in the sterilizing process; and its original vitamin C is retained indefinitely after opening. Because of its sterility, uniform consistency and wide availability, it can be used in infant feeding unqualifiedly, and may be formulated as whole *bottled* cow's milk.

Group II: Evaporated Milk

This milk, defined and regulated by the Food and Drug Definition and Standard, is a sterilized, homogenized sweet cow's milk evaporated

to one half its volume or to such a point that it contains not less than 25.9 per cent of total milk solids.

Its distinct advantages are found in the following features: *uniformity of composition* because of the pooling from many milk sheds; *low curd tension* (0) due to the heat treatment and sterilization in the evaporation process; *homogenization* of the fat; *hypoallergenic properties* induced by the coagulation of the soluble whey proteins which are less likely to be absorbed than the soluble allergic-potential protein whey; and the *universal availability* and stability in the can, facilitating its distribution all over the world.

Evaporated milk is one of the milk products used in the stock formulas in the newborn nurseries of many hospitals, and many physicians of long experience prescribe this milk as a basic mixture in their infant feeding practices. There are *42 companies* manufacturing over *460 brands* in *180 plants*. It would seem superfluous and an affected gesture to have a physician designate one brand as *best*, or to change from one brand to another to adjust an infant's specific feeding problem. By definition, origin and control there is uniformity in all brands, as government control specifies.[7] Any stated, explicit, *clinical* advantages of one brand of evaporated milk over another for infant feeding are specious inferences, and imply wishful illusion rather than scientific integrity.

Group III: Premodified (One-Formula) Dried Milks

Like the alchemists of old whose serious efforts were directed toward synthesizing gold from baser metals, so have child nutritionists and manufacturing chemists sought constantly for an artificial mixture which would be the exact nutritional counterpart of human milk. The modern attempts have been attended with comparably better success. The intangible "something" which human milk possesses has not yet been placed securely in a bottle or can for use by infants.

The advantages of these milks may be listed: They are geographically available almost everywhere in the civilized world, and their keeping qualities are constant within reasonable limits; they are uniform in composition; easily prepared and readily soluble by simply adding water or any diluent; they have a low curd tension because of the desiccating or evaporating processes used in their preparation; and a dubious advantage is that they may contain added vitamins, minerals and sometimes questionably necessary additives (possibly to favor the sales department of that product with an additional talking point, or to make a doubtful comparison with a similar competitive preparation).

The only limitation to their almost complete substitution for human milk or other milk mixtures for all babies lies in the fact that they are

complete one-formula foods with no flexibility to adjust to a given infant's specific requirements. No ingredient can be removed or added without disturbing the intended chemical structure of the end product. In a small proportion of infants the digestion of certain elements is in question (more or less carbohydrate, less fat, higher caloric needs, softer or harder bowel movements). Infant feeding other than in breast feeding is still an individual problem, and adaptability of composition is often desirable.

Any of these premodified milks are ideally used as complements and supplements to breast feeding. They may be subdivided into three classes: *whole milks, low fat milks* and *fat-substituted milks*. The proprietary products available in this country and Canada belonging to this group are Alacta, Baker's Modified, Biolac, Bremil, Dryco,* Hi-Pro, "Humanized," Klim,* Lactogen, Lactum, Olac, Powdered Whole,* Similac, and SMA-Powdered.

Group IV: Premodified (One-Formula) Liquid Milks

These milks are like their *dried* or *powdered* counterparts in that they are also *complete* mixtures needing only dilution with water and, with some, the addition of a carbohydrate. Apparently the parent-customers find them advantageous because the minor problem of rendering the mixture soluble in the diluent is easier than with the dried product. Most of the companies manufacturing this class of premodified milk products also have a preparation in the powdered form (*Group III*), or have the analogous dried mixture which they offer here in a liquid state. This group of milks is apparently a matter of commercial competition with utility in mind, rather than a nutritional necessity.

All that has been said of the previous category is also applicable to this group of milks, for most of them are the liquid parallels of a dry product. The proprietary preparations in this group are Baker's Modified, Biolac, Dalactum, Dextrogen, Eagle Brand Condensed, Lactum, Similac, SMA Concentrate and Varamel. (The last-named product has no added carbohydrate, but may be supplemented if necessary in formulation.)

Group V: Protein Milks (Albumin Milk, Eiweiss Milk)

This type of milk is placed in a separate category from the powdered milks because of its especial character and clinical use. It is essentially a partially skimmed lactic acid milk to which have been added the curds from whole milk obtained by rennin digestion. It has a low buffer value,

* Those marked with an asterisk are whole powdered milks with no carbohydrate added.

little of the whey salts, and is a poor culture medium for the fermentable bacteria. The high casein content favors the production of formed stools, the curd is fine-grained, the mixture is acid, and the fat content is low—all of which advantages render it an ideal combination for digestion by any infant.

Specifically, *protein milk* is useful in the celiac syndrome when there is an intolerance to fats and sugars of conventional milks. Protein Milk is definitely a special nutritive agent, and has enjoyed the confidence of physicians as a necessity in their armamentarium of infant foods. It is not to be confused with the preparations known as *protein supplements*. The merit of the former lies in the physiologic role of the predigestion of the curd, rather than in the chemical characteristics of the chemical composition, as is true with the *protein supplements*.

There are only three of these products available commercially: Powdered Protein Milk (Mead, Johnson), Powdered Protein Milk (Cow & Gate, Canada) and Protein SMA-Acidulated (Wyeth).

Group VI: Hypoallergenic Milks

Since the allergenic factor of infant foods is found most often in the protein component, it is logical that extensive efforts have been directed toward the role of specific foods involved in this hypersensitivity.

The protein molecule in the milk lactalbumin often is identified as the allergenic agent, and *changing to the milk protein of another animal species* than that of the cow is one way by which this sensitivity may be combated. Another method is by invading the vegetable kingdom and *substituting a vegetable protein* for that of an animal protein. By still another process, that of *changing the structure of the protein molecule by heat treatment*, the milk is made less allergenic. Any of these methods summarizes briefly the techniques utilized by the fresh and proprietary food industries in solving this common and ubiquitous problem involved in food allergenicity in infants, whether the discriminating food is the offending agent in eczema, asthma or a gastrointestinal manifestation.

There are more products in this group than in any of the others, possibly illustrating the long-observed medical axiom that the diseases or entities which are least specifically defined are accompanied by the greatest number of therapeutic agents. The proprietary preparations available to help combat the allergic states in infancy are Allerteen, "Allergiac," Almond Lac, Dale Dehydrated Goats' Milk, Capri Evaporated Goats' Milk, Meyenberg Evaporated Goats' Milk, Hypo-Allergic Powder (Hypo-Allergic Liquid is discontinued), Gerber's Concentrated Meat Base Formula, Mull-Soy Liquid, Mull-Soy Powder, Nutramigen, Sobee Powder, Sobee Liquid and Soyalac. The products Hi-Pro and

Evaporated Milk listed in other groups may also be mentioned in this class.

Group VII: Acid Milks

Acid milks have had their popularity during the various phases in the history of infant feeding as well as in certain provincial areas of our country, the latter reflecting apparently the respective medical school origin and training of the respective physicians using these milks as standard or basic formulas. Acid milks have been demonstrated to have the same "therapeutic" properties as buttermilk, the peculiar virtues of which have been recognized for many years. It may be prepared either by culturing or souring fresh milk, or by adding an acid to fresh or evaporated milks. *Lactic acid* has always been favored for this purpose and has been used more consistently than other acidifying agents. *Lemon juice, orange juice, pure citric acid, acetic acid, cider vinegar* and *hydrochloric acid* all have been used for this purpose. There is no striking difference clinically in the use of any of these acids, but lactic acid is generally conceded to be the favorite. *Dried lactic acid milk powders* are the most convenient as well as the most efficient preparations of this type of milk and are the ones most generally used at present.

Acid milk is so much more readily digested than sweet fresh cow's milk that it can be given in greater concentrations and larger amounts than other milks. It is especially indicated for infants who are undernourished and need a relatively large amount of food, for those who will take only a small amount at one time, or those whose digestion is impaired or inadequate. The major factor in its greater digestibility lies in the virtue, as with buttermilk, that it does not recoagulate in the stomach. Another advantage is that the carbohydrate added may be in larger amounts (up to even 7 per cent) than in conventional mixtures (only up to 3 to 4 per cent).

The proprietary dried acid milks available are Pelargon (Nestlé), Powdered Lactic Acid Milk (with Dextri-Maltose added) #1 and Powdered Lactic Acid Milk #2 (both Mead, Johnson), Skimmed Lactic Acid Milk and Whole Powdered Lactic Acid Milk (both Borden), and Powdered Lactic Acid Milk (Cow & Gate).

Group VIII: Protein Supplements

Protein deficiency in infants may develop because of insufficient intake of protein food, impaired digestion or absorption, unusual loss of protein from the body, or an increased breakdown of body tissue protein. There are now various protein supplements available to adjust for this deficiency of body protein. As the term "supplement" indicates,

they are *added* to the usual expected intake of food rather than regarded as food substitutes.

When the digestion and absorption are *not impaired* and additional protein is needed, complex proteins may be supplied *in excess* of the dietary protein. The commercial preparations available for this need are Casec, Gerilac, Lonolac and Protenum.

If the digestive functions of absorption and utilization of protein are *impaired* (diarrhea—acute or chronic); when *low residue diets* of high protein content are required (chronic enteritis); when there is *an immediate need* for larger amounts of protein than can be assimilated in intact protein (postoperative protein depletion); and when *tube feeding* is indicated—these situations may be met by supplying predigested protein broken down to the simplest units of protein absorption—*peptones* and *amino acids*. The various products at hand to fill this need are Lactimin, Peptalac, Protolac, Protolysate and Protinal Powder.

It should be emphasized again that *in no way are any of these products akin in form or function to* Protein Milk.

Group IX: Skimmed Milks

The only excuses for classifying skimmed milks in a separate group are that they are physically identical, and that their uses are common to each other. They vary only in that they may be liquid or dry, and that the fat content may be between a trace and 0.2 per cent. It is important to remember that the curd of skimmed milk should be softened as with whole milk, which is achieved by boiling, drying, evaporating or by enzyme addition. It differs from whole milk in that the fat is wholly or partially removed. The vitamin A of any milk is contained in the fat fraction and should be replaced, as it is in most of the following proprietary skimmed milk products available: Powdered Skimmed Milk (Borden); Powdered Skimmed Milk, Powdered Partly Skimmed Milk, Skimmed Milk Concentrated (evaporated) and 50% Skimmed Milk Concentrated (evaporated) (all Cow & Gate); Kim (evaporated), Mello-Lac, Starlac, Carnation Non-Fat Dry Milk Solids and Pet Non-Fat Dried Milk Solids. There are probably other dried and liquid skimmed milk products on the market, but the ones listed here are said to be designed for infant feeding especially.

Therapeutic Adjuncts and Dietary Supplements to Infant Feeding

There are other preparations available for infant feeding which cannot be classified strictly as foods, but rather as therapeutic agents, and yet they stem from food origins. They are presented here by name and description because their uses are concomitant to conditions for which

specific infant foods are used. They also employ principles which are fundamental to foods listed in the preceding nine groups.

Apella is a highly concentrated and dehydrated *apple powder* containing 5.2 per cent *pectin*. It is used as an agent in acute and chronic diarrhea, in conjunction with the milk formula or other foods.

Arobon is the processed pulp of the Carob bean used in the treatment of specific and nonspecific diarrheas. The value of this product is said to be due to the high content of *legnin, pectin* and *tannic acid*—all inherent in the natural product.

Casec may be considered a milk food as well as an adjunct in this present category. It is *calcium caseinate* made from the curd of skimmed milk and lime water. It contains 88 per cent *protein* and 1.6 per cent *calcium*, and may be regarded as a supplemental source of these substances when needed. Casec is also a useful agent when the abnormal feeding situation does not require radical measures, as in the milder diarrheas of parenteral origin, when it may be added to the normal formula or between feedings.

Probana is a uniform blend of Powdered Protein Milk, Proteolysate, *banana powder* and *dextrose*. It is a therapeutic food especially designed for infants and children with impaired pancreatic function, for infants surviving operation for meconium ileus, and in chronic diarrheas and food intolerances of the first six months of life.

Protoban may be considered a dietary supplement or complete infant food rather than a therapeutic agent. It consists of *skimmed milk powder, lactalbumin*, specially processed *soybean protein, ferrous gluconate*, and the carbohydrates of *dextrose, maltose* and *sucrose*. Among the pediatric indications of Protoban are the treatment of celiac disease and certain diarrheal disorders; the treatment of nutritional anemias; augmentation of the protein component of diet in malnutrition; and supplementation of the diet of patients with certain allergies.

Soyola is an "emulsion of *soybean oil* and *rice bran concentrate*" for use in eczema. It exploits the observation that most infants with intractable eczema have a low serum, fatty acid iodine number. One of the primary essential unsaturated fatty acids is *linoleic acid*, found in large amounts in soybean oil, which is the base of Soyola. It may be administered with the milk formula or with any food supplement.

CARBOHYDRATE ADDITIONS AND MODIFIERS

It would not be feasible in this paper to elaborate on each of the 27 carbohydrate additions and modifiers listed for infant feeding in this country. A full description of each with the chemical composition and prescribed uses may be found in the text referred to in the References.[14] It will suffice here to mention a few generalizations as to their origin and theory of their respective uses in infant feeding, and to list the commercial products available.

Classification as to Physical State and Origin

The carbohydrate additives and modifiers may be at once classified into *liquid* and *powdered* preparations. This obvious physical division is not of much consequence except in the facility of measuring them, in their ease of solubility and in the computation of calories and percentages.

A further division may be made on the bases of their origins and precursors, or, more simply stated, the complex carbohydrate (starch) from

which they are obtained. The methods used for these processes are usually by *acid hydrolysis* or *diastase fermentation*, or some variation of these two procedures. The following is a list of the complex carbohydrates or starches from which the various carbohydrates are obtained: *potato, cornstarch* (and, from this product, *corn syrup*), *corn flour, tapioca,* the grains of *wheat* and *barley, banana, apple, whey of cow's milk, sugar beet* or *sugar cane* (and their by-product *molasses*), fruit sugar of any blossoms, which is *honey*.

Theoretical Concept of Carbohydrate Digestion

For those who are confused by the multiplicity of the various components of starch found in the equally numerous proprietary sugars available, this brief and generally accepted theory will help clarify the confusion. It would seem logical to present to the infant gastrointestinal digestion the simplest monosaccharides for immediate absorption, and have done with the intervening steps of digestion from a higher to a lower order. This was not Nature's intent, however direct and efficient it may seem.

The plan appears to be that there is a natural economy in carbohydrate digestion—that each *amylolytic enzyme* must be used. The reduction of *starches* into *dextrins*, into *disaccharides* (maltose, and so on), into *monosaccharides* (dextrose, and so on) must go on, apparently to utilize all the digestive enzymes provided for this purpose. For this reason most of the carbohydrate additives consist of the varied higher components presented to the digestive apparatus for reduction. Therefore, in most commercial modifiers, polysaccharides and disaccharides are present at once in varied proportions as well as any of the split products of a lower carbohydrate order, and may be used for specific purposes. Those with larger amounts of dextrins naturally inhibit fermentation. When there is not enough fermentation, when the stool is soapy or firm, or when the stool is excessively putrefactive, one of the modifiers high in a fermentable sugar, such as *maltose*, is indicated.

Review of Sugar Additives

Varied claims have been made for each of the integral carbohydrate components of digestion, but in general it is safe to say that it matters little from whence the carbohydrate was obtained, how it was reduced from the raw product, or as to the content of the various reduction entities except as they are found to remain in ratio to each other. Anyone who becomes didactic on any of these points will be supported by many clinical proofs and laboratory data. Anyone else who wishes to refute the position as to the greater value of one carbohydrate component over

another will also have available adequate proofs in the literature. It appears, then—for the *normal* infant digestive tract,—that all the commercial carbohydrates now to be listed are adequate for their specified purposes, the guidon being the simple physiologic principles of digestion mentioned at the beginning of this section.

The carbohydrate additions and modifiers available for use are as follows: Alerdex, Kanana Banana Flakes, Beta Lactose, Cane or Beet sugar, Cartose, Dexin, Dextri-Maltose #1, Detri-Maltose #2, Dextri-Maltose #3, Dextri-Maltose with Yeast Extract and Iron, Pectin-Agar in Dextri-Maltose, Dextrosol, Hidex, honey (strained), Karo Syrup (red label—White; blue label—Dark), Lilly White Corn Syrup, Crown Brand Corn Syrup (dark), Lactose, Malose, Malt Soup Extract (liquid), Dri-Malt Soup Extract, Mellin's Food, Meloripe Banana Powder, molasses (light and dark) and Sweetose.

Milk Mixtures *Without Added* Carbohydrate

There is an expanding interest and literature on the subject of infant milk mixtures *without added* carbohydrate. This variation is not new. It is recognized as one of the earlier eras in the history of infant feeding, and was widely practiced in England and France during the last century. It is apparently part of a cycle to which infant feeding is returning, a "vogue" as one finds in many other phases of medicine. There are numerous reports recently of many thousands of infants who have been fed by this method with satisfactory nutritional results, as noted by the reports in the literature on this subject.[10]

No valid reason is apparent why this method of infant formula construction has not been more widely accepted and used, if it is as adequate and simple as the investigators have found. It may be at present an innovation, with no concerted effort to disprove it. It is also a deviation from an established convention, which is normally resisted when precedence has been established.

The scientific evidence in favor of adding carbohydrates to diluted cow's milk, or in fortifying premodified milks, is weighted with better reasons than empiric custom and tradition. Uncomplicated calculation and simplicity in formula construction may be the modern watchwords, but nutritional data point to values more important than these. The following accepted roles for adding sugars to milk mixtures for the feeding of infants have long been credible and accepted by nutritionists: it permits *normal metabolism of fat*, allows *protein to be used to build new tissue* rather than to provide calories (protein-sparing effect), encourages *normal water balance* which acts as an added safety factor against dehydration, *reduces the water excretory capacity* of the immature kidney of the infant, *influences electrolyte balance* and points up a

relationship among carbohydrates, sodium and potassium not yet clearly defined.

A clinical value has been observed by many practitioners of infant feeding which is of importance. Babies who receive no carbohydrate in the milk mixture appear to be hungry and dissatisfied with their food. When the same formula is fortified with sugar, they are happier and much more content. Other clinical advantages are that greater weight gains are noted which may be interpreted as being beneficial if used in reasonable proportions, the sugars are inexpensive and easily available, they are readily digested and are high in energy sources. A still more practical advantage is the use of the carbohydrate in the formula to affect the character of the stool, whether loose or too formed.

The excuse for devoting an unusual amount of space to this subject is based upon the fact that it is apparently a "fashionable" trend in infant feeding at present. Therefore it might be well if the reader becomes informed on a new deviation of an inevitable cycle which this phase portends. It may be that much of the success in any change from conventional procedure in infant feeding in the present day may be credited to the custom of beginning solid food supplements so early in the first year as is now practiced. The fortified, precooked cereals are offered as early as the sixth week, and soon are followed by vegetables, egg yolk and fruits. Any deficit that might otherwise be noted in the milk mixture is adequately supplemented by these accessory foods, and thus success can attend almost any deviation or deficiency in the milk formula.

CONCLUSIONS ON PROPRIETARY FOODS

Multiplicity and duplication are apparent in the infant feeding field, which is not reprehensible, but only confusing. It is a characteristic of any phase of competition in private enterprise and American industry, whether it be in automobiles, house furnishings, dairy products or entertainment. This peculiarity of "the American way" offers a healthy check on monopoly and stimulates better products within that respective commercial venture.

From the wide array of milk foods produced by competitive commercial enterprise, a classification is possible, and any interested physician may be oriented by arranging the foods into categories as listed here, or by any he might wish to make for himself. A suggestion is made to the practitioner who is dismayed and confused by the many products available: *Choose one or two of the products in each of the groups of available foods. Become acquainted with their chemical composition, methods of formulation and clinical utility.* The smaller variations between the remaining products of any group will not be of any striking importance which would impugn the physician's scientific integrity, nor

would it deny anything from the most discriminating infant digestion. These selections might be changed to one or two others from time to time, and thus eventually an acquaintance will be established with most of the available preparations. Still another suggestion might be added—that an outline of *the functions and general compositions of each group be kept in mind so that when any new product appears on the market, an evaluation of its worth and classification will be immediately apparent.*

Comment on Controversial Concepts of Infant Feeding

The field of infant feeding is at present involved in the turmoil between the older orthodox "scientific" approach to feeding instruction and the "liberal" attitude which presumes that too much is made of *exact* nutritional needs of the infant, and that wider tolerances are to be accepted and taught. Neither extreme is completely tenable at present. As usually occurs, a compromise will accrue from this conflict of opinions, contributing the best principles of both concepts.

When a paper appears in the literature attempting to review and summarize known information of an applied sort in infant nutrition, the proponents of the liberal school critically observe that detailing data in this manner emphasizes an unnecessary *precision* of feeding rules and concepts. *Just the opposite implication is intended.* There will always be the neophyte to instruct, and the older physician to orient who has had painfully to unlearn many of the truths of nutrition he was taught. Even if the premise is accepted that a thorough foundation in biochemistry for medical students is the best preparation for the ultimate application of nutritional principles, the students' discrimination is dulled by the welter of commercial products and "deluge" of information which they meet upon emerging from the sheltered haven of medical school laboratories and the children's wards of hospital internship. Without an occasional orientation the younger physician may flounder about, unable to apply the truths he was taught. By trial and error he may make some erroneous decisions in an effort to counter the slanted commercial information directed at him, and later may develop unsatisfactory habits in his infant nutrition prescribing.

Lay parents of infants in this modern controversy are not unaffected. The casual directive of "Give the baby some milk with a little water and a bit of sugar—any kind will do" leaves the parents in a most confused and uncooperative mood. They too have been the victims of a recent authoritative era and reflect all the dogmas which have surrounded their lives. They want and demand more exact information and instruction. It will be many years before the complacency and assurance of the liberal school will be indoctrinated into modern pa-

rental concepts of "scientific baby care" with which the parents are bombarded on every side. This is reflected in attitudes of pediatric care in the private office versus the clinic manned by full time staffs. The private physician is said to make a "production" of his infant feeding care, studiously raising or lowering the sugar in the formula by one teaspoonful, or by adding the solid food supplements to the dietary regimen "much too early" and thereby impressing the mother by unnecessary gestures which are nutritionally unsound.

It has been proved that the infant digestion is less exacting and more tolerant of excesses than was formerly presumed or accepted. These newer variations have been made possible not entirely by the strides made in the chemistry of nutrition, or by the boldness of prescribing physicians. Many "homely" assists have been given to infant feeding of the present day by such factors as the availability of bacteriologically clean milk, modern refrigeration in the home, sanitary plumbing and pure water supplies, efficient sewage disposal, modern sterilization techniques, widespread education of hygiene concepts, and other accoutrements of the modern standard of living. All these factors have contributed to the present high level of infant nutrition as we find it today.

SUMMARY

The essential historical facts necessary for an understanding of the evolution of modern infant feeding achievements are here outlined. The elementary and chemical data necessary for interpretation of nutritional requirements in formula computation are reviewed. A classification of all 77 fresh and proprietary infant milk foods and 27 carbohydrate modifiers is suggested, with a definition of each group and a statement as to the function and utility of these classes of foods. There is a listing of the proprietary products by name into the groups to which they belong. Comments are made on the multiplicity of these foods, and suggestions presented as to how these foods may be used to the best advantage of the prescribing physician, as well as of the infant consumer.

It is hoped that this exposition will help span the gap between the laboratory science of *infant nutrition* and that of applied clinical *infant feeding* for the physician who is faced with these problems in his daily infant feeding practice of formula prescribing.

REFERENCES

1. Abt, I. A., ed.: Pediatrics. Philadelphia, W. B. Saunders Company, 1923, Vol. II.
2. Brennemann, J., ed.: Practice of Pediatrics. Hagerstown, Md., W. F. Prior Company, 1948, Vol. I.
3. Clements, F. W.: Infant Nutrition. Baltimore, Williams & Wilkins Company, 1949.

4. Committee Report: Methods of Determining the Curd Tension of Milk. J. Dairy Sc., 24:825, 1941.
5. Council on Foods (American Medical Association): Nutritional Significance of the Curd Tension of Milk. J.A.M.A., *108*:2040, 2122, 1937.
6. Evans, P. R., and MacKeith, R.: Infant Feeding and Feeding Difficulties. London, Churchill, Ltd., 1951.
7. Federal Food, Drug and Cosmetic Act. Washington, D.C., Federal Register, Nov. 22, 1941, Sec. 403 (j).
8. Glaser, K., Parmelee, A. H., and Hoffman, W. S.: Comparative Efficacy of Vitamin D Preparations in Prophylactic Treatment of Premature Infants. Am. J. Dis. Child., 77:1, 1949.
9. Grulee, C. G., and Ely, R. C.: The Child in Health and Disease. 2d ed. Baltimore, Williams & Wilkins Company, 1953.
10. Harris, L. E.: Infant Feeding with and without Added Carbohydrates. Am. J. Dis. Child., 82:677, 1951.
11. Jeans, P. C., and Marriott, W. M.: Infant Nutrition. 4th ed. St. Louis, C. V. Mosby Company, 1947.
12. Lanman, J. T.: Modern Trends in Infant Feeding. Scientific Report No. 14. New York, Sugar Research Foundation, Inc., 1952.
13. Levinson, A.: Pioneers of Pediatrics. New York, Froben, 1943.
14. Meyer, H. F.: Essentials of Infant Feeding for Physicians. Springfield, Ill., Charles C Thomas, 1952.
15. Robinson, E. L., and Thompson, W. L.: Effect on Weight Gain of the Addition of Lactobacillus Acidophilus to the Formula of Newborn Infants. J. Pediat., 41:395, 1952.
16. Ruhrah, J.: Pediatrics of the Past. New York, Paul B. Hoeber, Inc., 1925.
17. Stearns, C., Jeans, P. C., and Vandecar, V.: The Effect of Vitamin D on Human Growth. J. Pediat., 9:1, 1936.

2236 Pratt Avenue
Chicago 45, Illinois

SUDDEN ILLNESS IN INFANCY

LEE FORREST HILL, M.D.

For the purposes of this paper the term "infancy" will be interpreted roughly as the period from the end of the neonatal period to age two years. The disturbances discussed will be those commonly encountered in the general practice of pediatrics. It will be assumed that the infants are in their homes and have been in normal health previous to the onset of the illness. Under these conditions most illness will be sudden in onset and minor in nature. Most will be self-limited infections involving the respiratory and gastrointestinal tracts. Occasionally, however, the physician will be faced with a more serious problem which may present diagnostic or management difficulties, either because of the nature of the illness itself or because of the peculiarities of infantile reactions to disease. It is with some of these disturbances that the present paper is concerned.

INFANTILE CONVULSIONS

It seems appropriate to start off the discussion of sudden illness of infants with consideration of infantile convulsions. The problem may be a simple one easily disposed of if the convulsion falls into the category of the simple "febrile" convulsion analogous to the chill experienced by an older child or adult at the onset of an infection. On the other hand, the convulsion may be a manifestation of an underlying organic brain disease or of a systemic disorder which may require extensive investigation to establish its etiology.

Acute "Febrile" Convulsions

Uncomplicated febrile convulsions usually occur within the first few hours following the onset of an acute infection, not infrequently at the

From the Raymond Blank Memorial Hospital for Children, Des Moines, Iowa.

end of a period of sleep. The fever is usually high, most often in the range of 103° to 106° F. taken rectally. The convulsion is likely to be of short duration—perhaps five to ten minutes—and will frequently be over by the time the physician arrives at the home. Physical examination may establish a clear-cut etiology for the fever such as an acute tonsillitis or pharyngitis, pyelonephritis, measles or scarlet fever. It is well to remember the relatively high incidence of convulsions associated with roseola infantum, the commonest of the exanthemas in children under three years of age. This diagnosis is suggested when the degree of illness appears to be less than one would expect from the height of the fever, and when only mild redness of the throat with slight enlargement of the cervical lymph nodes is found on examination. If the white blood cell count shows a leukopenia (3000 to 6000 cells) with a preponderance of lymphocytes, it is reasonably safe to predict that the infant will break out with a measles-like rash after subsidence of the fever on the third or fourth day of the illness.

Consideration should be given to the view expressed by some that a spinal tap should be done in every child who has a convulsion accompanied by fever in order to avoid overlooking a bacterial meningitis for which there is a specific treatment. Unquestionably this is the safest rule to follow, and if there is any doubt about the etiology of the acute infection or any suspicion, from the physical examination, of central nervous system involvement, spinal puncture should be done. Practically, however, there are many instances of acute febrile convulsions of short duration in which the etiology of the infection is so obvious that spinal puncture seems unnecessary.

A family history of similar convulsive episodes in a relative during infancy lends support to a diagnosis of an uncomplicated febrile convulsion in the patient. Parents should be warned of the likelihood of a recurrence of a convulsion with subsequent acute infections, but should be assured that, with advancing maturity, the child will in all probability outgrow them and will be none the worse as a result of their occurrence. However, there is evidence that some 10 to 20 per cent of infants and young children who have febrile convulsions, later have spontaneous convulsions without fever. To this extent the prognosis to parents for ultimate "outgrowing" of the convulsions should be guarded.

Convulsions Differing from the Acute Febrile Type

The situation is quite different when the pattern of the convulsive episode differs materially from that described for a simple febrile convulsion. For instance, the convulsion may not be accompanied by fever, or it may be accompanied by fever, but be of long duration—30 minutes to an hour or even longer—or it may follow the onset of fever by a day

or so, or even come on after the febrile course is over. It may be repeated several times or have occurred frequently on previous occasions. Here a "convulsive work-up" is mandatory, for the etiologic possibilities are numerous. It is beyond the scope of this paper to list and describe each of these possibilities. However, it may be of interest to list the diagnostic procedures which should be included in a reasonable work-up, and to indicate the reason for each procedure.

The Convulsive "Work-up." Clearly, a detailed history of circumstances preceding the onset of the convulsion is of first importance. This should include an inquiry into the family background, into any untoward events occurring during pregnancy such as infections (German measles) or exposure to radiation in the first trimester, and especially into the details of the delivery and subsequent happenings during the following week or ten days. A history of difficult resuscitation or of a mild convulsive episode on the second or third postnatal day may be the only clue to the etiology of later-occurring convulsions, even after an exhaustive work-up has been completed. Equally important is the postnatal history. Did the child ever have a head injury or an illness in which he was unconscious? Is there any chance of his having ingested an unknown substance which might contain strychnine or some other convulsant substance? Has he recently been given pertussis vaccine or been vaccinated against smallpox? Has he routinely been given vitamin D? The more painstaking the history, the more likely that a satisfactory explanation for the convulsions will be forthcoming.

Next in order is the physical examination. As a part of a careful physical and neurologic evaluation, the eyegrounds should be examined for choking of the disks, retinal hemorrhage, and the cherry-red spot at the macula as seen in Tay-Sachs or Niemann-Pick diseases. Remember that infants in the first few months of life with infections of the central nervous system may not show the usual signs of meningeal irritation exhibited by the older child such as nuchal, back and hamstring rigidity. More important is the status of the fontanel. If it is tense and bulging, one may be certain that there is increased intracranial pressure. Routine is an initial blood cell count and urinalysis, the purpose of which is obvious.

Of the special types of examination, the spinal tap is the first to be done. Its purpose is, of course, to exclude the possibility of an infection of the central nervous system—either bacterial or viral—and also to measure the pressure of the fluid. Rarely, a grossly bloody fluid might indicate subarachnoid hemorrhage from rupture of a defective blood vessel such as a congenital aneurysm. More often a bloody tap in an infant is the result of local trauma. Bilateral subdural taps should be done if the history and physical examination suggest the possibility of a subdural hematoma. Previous vomiting plus the finding of retinal

hemorrhages and a head size larger than normal point strongly toward this possibility.

A roentgenogram of the skull serves two useful purposes: first, to determine whether the sutures are separated abnormally as in increased intracranial pressure from hydrocephalus or tumor; and, second, to reveal cerebral calcification. The latter is found in several diseases which occur in the age period under discussion, among the most important of which are congenital toxoplasmosis, tuberous sclerosis, cytomegalic inclusion body disease, craniopharyngioma, tuberculoma, hematoma and the Sturge-Weber syndrome. If plumbism is suspected, a roentgenogram of the long bones may be diagnostic by showing the characteristic lead line at the growing ends.

The convulsive "work-up" should also include a fasting blood sugar, serum calcium and phosphorus and a blood urea or nonprotein nitrogen determination. The finding of hypoglycemia, hypocalcemia or an elevated blood urea nitrogen or nonprotein nitrogen would suggest an extracranial etiology for the convulsion, and would require further investigation to establish the cause of the abnormal value. Hypoglycemia occurs with glycogen storage disease (von Gierke); hyperinsulinism from an islet cell tumor of the pancreas or from parenteral administration of excessive insulin; severe liver disease, as is sometimes seen in infectious hepatitis, adrenal and pituitary insufficiency; or the hypoglycemia may be functional or idiopathic in origin. Hypocalcemic tetany occurs when the ionized portion of the serum calcium is reduced below the convulsive threshold. Clinical states are tetany of the newborn, rickets due to vitamin D deficiency, celiac disease, hypoparathyroidism and pseudohypoparathyroidism. Tetany also occurs in alkalosis from excessive ingestion of an alkali such as sodium bicarbonate, from loss of chloride as in vomiting from high intestinal obstruction, and from hyperventilation. An abnormally elevated blood urea nitrogen or nonprotein nitrogen indicates renal disease such as acute glomerular nephritis or congenital malformation of the urinary tract.

Not infrequently the physician proceeds thus far in his convulsive work-up and still has no answer to his problem. He has four additional methods of study to call upon if reasonable indications exist. These are electroencephalography, ventriculography, pneumoencephalography and arteriography. An abnormal electroencephalogram in an infant with convulsions of obscure etiology may be helpful in suggesting that prolonged anticonvulsant treatment should be instituted. Under these circumstances it is assumed that the infant either has idiopathic epilepsy or has suffered brain injury somewhere along the way sufficient to set up an abnormal focus of electrical discharges. The injury to the brain may have occurred in utero, paranatally, or after birth from infections, toxic agents or trauma. These infants should be treated with appropriate daily

doses of anticonvulsant drugs such as phenobarbital or Dilantin for three to five years. If no further convulsions have occurred in this time, cautious withdrawal of the drug may be considered.

Ventriculography outlines the ventricular system and reveals dilatation, displacement and obstruction. It is done in preference to pneumoencephalography whenever obstruction exists or is suspected along the ventricular pathways. Pneumoencephalograms may be helpful in demonstrating such abnormalities as cerebral atrophy or agenesis. Arteriography outlines the cerebral vascular system.

Though the investigative work-up as outlined is by no means exhaustive, it is sufficiently comprehensive to permit the physician to reach a reasonable conclusion in the majority of instances. Furthermore, up to the point of the special neurologic procedures such as air study and arteriography, the studies can be carried out by the practicing physician himself.

DIFFICULT BREATHING

A second problem occurring frequently in infants is the sudden development of difficult breathing. This may be due to spasmodic croup, which characteristically comes on at night and is gone in a few hours. Or it may be due to acute laryngitis, a disturbance less dramatic in onset and of longer duration, but usually self-limited over a period of two or three days unless due to diphtheria. The latter has become nearly obsolete with practically universal diphtheria prophylaxis; nevertheless it should always be thought of in any laryngitis which persists longer than 24 hours and in which the signs of laryngeal obstruction are increasing. Exclusion by direct laryngoscopy is imperative unless diphtheria antitoxin in therapeutic dosage is administered. Rarely, a foreign body may lodge in the larynx and produce dyspnea. Obviously, any suspicion of such an event calls for direct visualization of the larynx. Pneumonia also may come on suddenly with its characteristic grunting respiration, but seldom offers diagnostic difficulties.

These, however, are not the types of respiratory distress that occasion the physician his greatest difficulty. More important in this respect are bronchiolitis, laryngotracheobronchitis and acute epiglottitis. Dissimilar in many ways, these three diseases nevertheless have certain common features which may make their differentiation confusing to those unfamiliar with their manifestations. Tracheotomy may be required in epiglottitis and laryngotracheobronchitis, but would be useless and even dangerous in bronchiolitis. The author recalls at least one instance when a tracheotomy was done in an infant with bronchiolitis with fatal result. Furthermore, epiglottitis and laryngotracheobronchitis are frequently of bacteriologic etiology and hence susceptible to specific therapy, whereas

the etiology of bronchiolitis is viral for which no specific therapy is available.

Bronchiolitis

Acute bronchiolitis (interstitial or viral pneumonitis of infants) is distinctly a disease of infancy, the majority of cases being seen within the first six months of life. In its typical clinical pattern it is infrequently seen after the age of two. Biopsies obtained from the surface epithelium of the posterior nasal pharynx by means of a swab show more than the usual number of inclusion bodies. Adams has suggested that bronchiolitis in infants and canine distemper may have a common etiology. Histopathologically, there is inflammatory thickening in the walls of the bronchioles, bronchi and interalveolar septums. The obstructed lumens permit air to enter, but interfere with its egress. The result is obstructive emphysema with symptoms simulating those seen in bronchial asthma. Clinically, the disease picture begins mildly enough with coughing and perhaps mild wheezing as the main symptoms. Progress, however, is rapid, and in a day or two expiratory dyspnea may be very marked. The fever may vary from little or none to as high as 104° or 105° F. Prostration at first may not be severe, but as effort continues, cyanosis and even extreme pallor may supervene. The cry is clear, and there is no stridor which would serve to differentiate the etiology of the dyspnea from that of laryngotracheobronchitis, in which the obstruction is subglottic and results in definite stridor. Bronchial asthma may be suspected, but no improvement is obtained with epinephrine. Furthermore, bronchial asthma is uncommon in infancy, but bronchiolitis is common. A further point of differentiation is the blood and nasal secretion eosinophile count.

Physical examination at the height of the disease in the severe case shows a distressingly sick infant. Respirations are rapid and grunting and accompanied by expiratory effort. Inspiration is short and expiration prolonged. Wheezing may be audible for some distance away, or little or no noise may be made. The percussion note is hyperresonant, and rales vary from a few squeaks to many of the fine and medium varieties. Although the accessory muscles of respiration may be in use, there is never as much suprasternal and infrasternal retraction as there is in laryngotracheobronchitis and epiglottitis. A roentgenogram usually adds little to what can be determined by physical examination. Obstructive emphysema is confirmed, and a few scattered areas of atelectasis may show in the film where a bronchus is occluded. Roentgenography and fluoroscopy are advisable, however, if for no other reason than to exclude the possibility of the obstruction's being due to a foreign body

in a main bronchus. Here the obstructive emphysema is one-sided, with the mediastinum displaced to the opposite side.

Treatment is best carried out in an oxygen tent with high humidity supplied from cold mist. Antibiotics are of no value against the virus, but should be used for their prophylactic value and on the chance that the etiologic agent may be susceptible to antibiotic therapy. If signs of cardiac failure appear, digitalization should be instituted. Fluids may have to be administered parenterally. In spite of a disease process of such ominous-sounding proportions, the prognosis for complete recovery is surprisingly good. In full term infants beyond the neonatal period the mortality rate is probably less than 5 per cent. Prematures and newborns have a more serious outlook.

Laryngotracheobronchitis

Acute laryngotracheobronchitis, occasionally referred to as Chevalier Jackson's disease because of his excellent description of the malady and his insistence that it be considered an entity, is most dangerous when it occurs in young infants because of its threat to life due to mechanical obstruction of the airway at a particularly vulnerable point. Tracheotomy is frequently imperative if the infant's life is to be saved.

Evidence indicates that the etiologic agent in laryngotracheobronchitis may be either bacterial or viral. Type b *Hemophilus influenzae* is the cause in some of the cases. This organism may be cultured from the nose and throat secretions or, better still, from swabbings taken directly from the larynx through the laryngoscope. It may also grow out in blood cultures. But whatever the pathogenic organism obtained, it should be tested for sensitivity against the various antibiotics and the appropriate antibiotic added to whatever was empirically instituted at the onset of the disease.

Pathologically, the disease produces an acute exudative inflammation of the larynx, trachea and bronchi and may even extend to the bronchioles. At first the secretions are mucoid, but later they become thick and tenacious and are expectorated with difficulty. Bronchial orifices become obstructed with pus or dried crustlike secretions, thus leading to atelectasis—a frequent, troublesome feature in the management of the disease.

Wide variations in the clinical picture are seen, but the more serious forms are likely to have a fulminating onset with rapidly progressing signs of laryngeal obstruction. The fever is high, usually in the range of 104° to 105° F., and the infants look and act sick. Illness stems both from the bacterial infection and from muscular effort expended in breathing. Stridor is present almost from the start. At first it is inspiratory, but it soon becomes both inspiratory and expiratory as inflamma-

tion and swelling occur below the vocal cords. The stridor and possibly hoarseness and aphonia are the chief differentiating points between laryngotracheobronchitis and bronchiolitis. Usually it is possible to make the distinction by merely looking at the patient. Other differentiating signs are the greatly increased sinking-in of the soft tissues at the upper and lower ends of the sternum with each inspiration which occurs in laryngotracheobronchitis, and the associated diminution in the intake of air which is in marked contrast to the obstructive emphysema of bronchiolitis. As would be expected, both coarse and fine moist rales may be heard over the chest, and, if a large bronchus has become obstructed with pus or dried crust, an area of atelectasis, easily confused with pneumonic consolidation, may be found. Restlessness from air hunger and cyanosis from anoxic anoxia may be present, but are not as ominous signs as is pallor, which denotes exhaustion and cardiac failure.

The crucial task in the *management* of an infant with severe laryngotracheobronchitis is timing of the tracheotomy. It has to be based upon clinical judgment and experience. So long as the patient is not restless, cyanotic or pale, it can be assumed that the tissues are being adequately supplied with oxygen even though respiratory difficulty is marked. But evidence of progression in the degree of obstruction as shown by increasing pulse rate, apprehensiveness and restlessness, and the onset of cyanosis or pallor indicate the need for prompt relief by tracheotomy. Needless to say, constant surveillance by an experienced person is of the greatest importance in selecting the time when the tracheotomy should be done. In an emergency a Mosher life-saving tube can be passed by the obstruction while preparations are being made for the tracheotomy. The "toilet" of the tracheobronchial tree after tracheotomy is a difficult and arduous task, but upon the skill and thoroughness with which it is carried out depends the patient's life. Suctionings must be frequent and effective in removing the thick purulent secretions and crusts which are prone to obstruct the bronchi with resulting atelectasis.

Acute Epiglottitis

Much less common than laryngotracheobronchitis is acute epiglottitis. *Hemophilus influenzae* appears to be the usual organism responsible for this disease. The organism may be recovered directly from the throat or from blood culture. Inflammation and swelling are confined to the epiglottis, aryepiglottic folds and the immediately surrounding structures. The onset of the disease is abrupt, as in laryngotracheobronchitis, with high fever, prostration, and marked difficulty in breathing. Since the obstruction is above the vocal cords, the dyspnea and stridor are inspiratory in type. Suprasternal and infrasternal retraction is as marked

as in laryngotracheobronchitis. In some cases the diagnosis can be made by simple inspection of the back of the throat. By pressing the tongue down the brilliantly inflamed, rigid, swollen epiglottis can readily be seen. Patients with the milder forms of acute epiglottitis may recover with oxygen, mist, an ice collar and intensive antibiotic therapy, but tracheotomy will be required for many.

Because of the rapidity with which the symptoms of respiratory distress progress in infants with bronchiolitis, laryngotracheobronchitis and epiglottitis, home care should not be continued too long. Though an atmosphere of moist air can be provided for the infant at home, it seldom is as effective as the cold mists available in hospitals. Antibiotic therapy can, of course, be as effective in the home as in the hospital, and so can the application of cold about the throat. But for oxygen therapy, which is most important, hospitalization is almost imperative. Furthermore, no infant with progressive signs of laryngeal obstruction should be allowed to go more than a few hours without ascertaining its cause. To do this, laryngoscopy and perhaps roentgenography are essential, and each of these is a hospital procedure. Finally, if it appears likely that a tracheotomy will be necessary, it is best to have the baby in the hospital under continual expert observation so that the optimum time for doing the tracheotomy may be selected, and the operation carried out in a dignified, unhurried manner with everything in readiness, rather than as a last-minute emergency scramble.

SUDDEN UNEXPLAINED FEVER

A third problem encountered by the physician in his pediatric practice—and a fairly common one—is the infant who becomes suddenly ill with unexplained fever. A good many years ago when the author was a medical student and later during the early years of his practice, the dictum in instances of unexplained fever in children was to "look in the ears and examine a urine specimen." This is still good teaching, but to it should now be added, "Do a spinal puncture, a blood culture and perhaps a bone marrow puncture."

The list of sudden febrile illnesses in which the etiology is not readily apparent after a careful physical exmaination and an adequate history is too long to include in its entirety here. However, it is desirable that those of more common occurrence and their peculiarities be considered.

Roseola Infantum (Exanthem Subitum)

Reference has already been made to roseola infantum and its frequent association with febrile convulsions. Its etiology has been proved to be

a virus, but its communicability is of low order, for in private practice one seldom sees a second case arising from a first. However, epidemics have been reported in orphanages and nurseries. As was stated previously, roseola is the commonest of the exanthems under three years of age. Characteristically, its onset is sudden with high fever and a minimum of prostration. The fever lasts three or four days and is abruptly followed by a measles-like rash first appearing on the trunk and spreading to the face and extremities. The rash is usually gone in 48 hours. Mild redness of the throat may be noted along with slight enlargement of the cervical nodes, yet the findings are extremely meager compared to the hyperpyrexia. Leukopenia and lymphocytosis are regularly found in roseola, and if these are present in an infant with symptoms as outlined above, a positive diagnosis can be made almost with certainty before the rash makes its appearance. It is surprising how frequently roseola continues to be misdiagnosed as measles. Its clinical pattern is so clearly distinct from that of either rubella or rubeola that confusion should seldom occur.

Pyelonephritis

Little need be said about the need for examining a specimen of urine for evidence of pyelonephritis in an infant with unexplained fever. Since girls acquire urinary tract infections with much greater frequency than boys, the ratio being about six to one, the finding of an appreciable number of pus cells in the urine of a boy justifies an investigation of the urinary tract by urine culture and by intravenous pyelograms. In the children's hospital where the author works, of 64 consecutive cases of pyuria in boys, 51 were found to have positive pathology. Surgery was required for 27. The problem is somewhat more difficult in girls for the reason that pus cells may have got into the urine from vaginal secretions during voiding. The issue can be settled promptly by obtaining a catheterized specimen from the bladder. If an abnormal number of pus cells is found, the urine should also be cultured, and the organism identified and tested for sensitivity to various antibiotics.

Some question may arise in girl infants with pyuria as to the necessity of doing an intravenous pyelogram. My policy is to do a pyelogram if the attack is of any severity. If it is mild and responds promptly to treatment within a few days, pyelography is usually postponed, pending the development of a second attack. In the hospital just referred to, 131 cases in girls with significant pyuria were studied by intravenous or retrograde pyelography, and 104 were found to have positive pathology. A final point that might be made about pyelonephritis is that treatment should be continued to the point of negative urine cultures rather than to the disappearance of the pyuria.

Otitis Media and Pneumonia

Perhaps the commonest cause for unexplained fever in infants is infection of the respiratory tract. Particularly is this true of otitis media and pneumonia. Infections of the respiratory tract between these two remote points usually manifest themselves by symptoms such as cough, or can be detected on physical examination. Examination of the ear drums in a young infant is often a difficult task because the canals may be small or occluded by cerumen, or both conditions may be present. For the practitioner the electric otoscope with its magnifying lens is a most satisfactory instrument. Most otologists seem to prefer a head-mirror and speculum. Small pieces of loosely attached wax can safely be removed by a curette, but large masses filling the canal are best removed by preliminary softening followed by gentle syringing with water. Finding of an inflamed ear drum in an infant with an obscure fever serves the dual purpose of focusing attention upon the respiratory tract as the probable seat of the infection responsible for the fever as well as upon the otitis media itself.

Most infections of the respiratory tract in infants manifest their presence by such symptoms as coughing and hence offer no diagnostic difficulties. An exception may be lobar or lobular pneumonic infiltrations due to one of the many types of pneumococci. Even careful physical examination of the chest may fail to yield any of the characteristic signs of pneumonic infiltration. The experienced observer may strongly suspect pneumonia by merely looking at the infant. Movement of the alae nasi and an increased respiratory rate are the chief signs that would arouse his suspicions. Confusing clinical findings in an older infant might be nuchal rigidity, indicating meningismus, or rigidity of the abdomen, drawing appendicitis or peritonitis into the differential picture. A white blood cell count in the range of 25,000 to 40,000 with a preponderance of leukocytes would point strongly toward pneumonia. A roentgenogram of the chest might well settle the problem by revealing a density of lobar or lobular proportions. If the roentgenogram is not conclusive, it may be necessary to do a spinal tap to make sure that nuchal rigidity is due to meningismus and not meningitis.

Appendicitis is uncommon in infancy and, when it does occur, is frequently difficult to diagnose until after perforation has occurred and a mass is present. As with appendicitis at any age, the most important single sign is localized tenderness in the right lower quadrant with muscle splinting or guarding of the underlying, inflamed appendix. In pneumonia the abdominal muscle rigidity is usually higher than in appendicitis, and localized tenderness in the right lower abdomen is absent. If, added to this, the fever and white blood cell count are high, it is most likely that pneumonia rather than appendicitis is the cause of the illness.

It is a wise precaution always to make a roentgen examination of the chest before subjecting an infant to an operation for appendicitis.

Meningitis

Reference has already been made to the fact that infants may not respond to infections of the central nervous system with the expected signs of posterior muscle rigidity. A recent case in the author's practice may be cited to illustrate this point.

An 8 months' old infant became ill during the night 3 days before admission. She was seen by the family physician on each of the next 2 succeeding days. No cause for the fever could be found, but antibiotics were administered. When seen at the hospital on the third day, the baby did not appear to be seriously ill. Her color was good, and feedings were taken reasonably well. The parents felt that the child was considerably improved over the previous day. She had vomited only once at the onset of the illness. Physical examination failed to reveal an adequate explanation for a fever of 3 days' duration. There was no nuchal rigidity, and Kernig's sign was negative. The fontanel unfortunately was closed. The white blood cell count was 19,000, with a preponderance of leukocytes. A roentgenogram of the chest and a urine specimen were both negative. The baby was admitted to the hospital for observation. Later in the day an intern examined the baby again and thought that she seemed somewhat stiff when set up. The resident was called and somewhat reluctantly did a spinal tap. The fluid was cloudy with some 3000 cells, mostly polymorphonuclears. No organism could be found in the stained smear, nor did one grow out in culture. However, response to therapy was prompt, and the baby made an uneventful recovery.

Such a recital yields two bits of useful information: first, that infants may have meningitis without the typical meningeal signs, and, second, that early administration of antibiotics in an obscure fever, especially if given in inadequate amounts, may have the effect of masking whatever infection is present, so that specific diagnosis is difficult or impossible.

Cases like that just cited are by no means unique in my experience. Clearly the lesson to be learned is that the source of an unexplained fever in an infant should be sought for as diligently in the central nervous system as in the respiratory or urinary tract. Obtaining cerebrospinal fluid for examination requires more effort than obtaining a urine specimen, a blood cell count or an x-ray film, but the effort may be rewarding.

Sepsis

This condition is mentioned here mainly to emphasize the importance of obtaining blood cultures in obscure illnesses of infants. Pathogenic organisms gain access to the circulation through lesions on the skin, through the umbilicus, and the respiratory and gastrointestinal tracts. Staphylococci, streptococci and organisms of the *Escherichia coli* group are the most common offenders. The symptoms and clinical manifestations of septicemia are markedly varied. There may be a fulminating

onset with fever, prostration, leukocytosis and little else of a localizing nature. A blood culture should always be a part of the work-up in a sudden illness of this type. On the other hand, there may be no fever, or the temperature may even be continuously subnormal, but the baby is lethargic, takes its feedings poorly, and fails to gain. Here again a blood cell count may show anemia and leukocytosis. With either type of onset the appearance of jaundice plus the finding of an enlarged spleen and liver is strongly indicative of septicemia. Isolation of a pathogenic organism from the blood stream is of great advantage in selecting the appropriate therapeutic agent.

PURPURA

A fourth manifestation of sudden illness in infants which may pose a problem for the physician is purpura. Occasionally the onset of the purpura is so clearly associated with a fulminating infection as to require little or no differential consideration.

Meningococcemia and Acute Adrenal Insufficiency

The outstanding example of this situation is meningococcemia with or without meningitis. When this is combined with symptoms of shock such as a cold, clammy skin, cyanosis, hypotension, a rapid, weak and thready pulse and perhaps coma, one can be certain that in addition to the septicemia with its toxicity, acute adrenal insufficiency has also occurred due to massive hemorrhage in the gland, or to necrosis (Waterhouse-Friderichsen syndrome). Progress of symptoms in this disease is extremely rapid, sometimes only a few hours elapsing from onset to death. Confirmatory laboratory determinations of adrenal insufficiency would be decreased sodium and chloride and increased potassium, together with a normal total circulating eosinophile count. However, there is usually insufficient time for these determinations to be of value in planning therapy.

The prognosis for meningococcemia alone is excellent, but, until recently, was nearly hopeless when it was complicated by acute adrenal insufficiency. However, some lives may be saved with the therapeutic agents available at present. *Therapy* should be directed at both the infection and the shock. An intravenous cut-down should be established immediately and a glucose and saline infusion started. Sulfadiazine and penicillin in appropriate amounts are given intravenously to combat the infection. Plasma or a blood transfusion should be switched in as soon as possible to improve the shock state. Norepinephrine should be added to the infusion to raise and maintain the blood pressure. One to 5 mg. of desoxycorticosterone in oil should be given to control the salt loss and

potassium retention. Finally, an intravenous preparation of hydrocortisone in a dosage of 50 to 100 mg. should be added to the infusion. If the child survives, suitable modifications will be necessary in the subsequent treatment to meet the child's needs.

Less dramatic and less of an emergency are the other forms of purpura which the physician is likely to encounter. Diagnosis can therefore be approached in a more leisurely fashion. It is customary to divide the purpuras into thrombocytopenic and nonthrombocytopenic types.

Thrombocytopenic Purpura

If the initial blood smear or an actual cell count reveals a marked diminution in the platelets, idiopathic purpura hemorrhagica immediately comes under suspicion. Prolongation of the bleeding and clot retraction times plus defective prothrombin consumption adds support to this diagnosis, especially if the peripheral blood examination shows no other abnormalities except anemia secondary to hemorrhage from the purpuric lesions. To clinch the diagnosis, however, bone marrow aspiration should be carried out and megakaryocytes demonstrated in normal numbers. In addition, cells of the granulocytic and erythrocytic series should also be normal. Even with these characteristic findings many physicians are loathe to make a positive diagnosis of idiopathic purpura hemorrhagica at the initial episode. With recurrence at a later date, little reason is left for doubt. Splenectomy is seldom advisable in the initial attack. Rarely, the disease may be so acute and fulminating, and response to a more conservative therapy so ineffectual, that removal of the spleen is justified as a life-saving measure. Usually, however, bleeding can be brought under control by transfusions of fresh whole blood as directly as possible from donor to patient, using special tubing and silicone-treated glassware to preserve platelets. When replacement of lost blood is not a factor, transfusions of platelets alone may be effective. This requires a special technique which is not available in most laboratories. Cortisone or ACTH is also useful in controlling the bleeding.

Thrombocytopenic purpura may be secondary to a variety of other conditions. Most to be dreaded among these is *leukemia*. Leukemia in infants is most often of the acute lymphatic type. It may be in either the aleukemic or leukemic phase. Usually the generalized adenopathy, splenomegaly, anemia and the finding of abnormal lymphocytes in the peripheral blood smear are sufficient to arouse suspicion. Positive diagnosis, however, rests upon bone marrow examination and the demonstration of an abnormal overgrowth by the immature leukemic cells.

Closely allied to leukemia as a cause of thrombocytopenia is invasion of the bone marrow by malignant tumor cells. Among the more com-

mon of these are such tumors as lymphosarcoma, Hodgkin's disease and neuroblastoma.

Aplastic anemia, either idiopathic or secondary to some chemical or physical agent, must also be included in the differential diagnosis in an infant with purpura and thrombocytopenia. Careful inquiry about any medicines the infant may have been receiving is important. The author has had two children come under his observation with aplastic anemia presumably due to chloramphenicol. Both children died. A number of other chemicals as well as x-ray and radium are known to inhibit hematopoiesis. The peripheral blood shows panhematopenia with no increase in the reticulocyte count. Again, bone marrow examination is essential for confirmation of the disorder.

More unusual causes of purpura and thrombocytopenia are hypersplenism and thrombotic thrombocytopenia.

Nonthrombocytopenic Purpura

When the initial examination of the blood in an infant with purpura reveals a normal number of platelets, attention is directed to a different etiologic consideration from that already discussed. The cause of the bleeding in nonthrombocytopenic purpura is vascular rather than platelet deficiency. Idiosyncrasy to drugs may cause this kind of purpura. It also results from vitamin C deficiency. In an infant with purpura who gives a history of inadequate vitamin C intake, a diagnosis of scurvy may be confirmed by demonstration of the characteristic bone changes in an x-ray film or by finding an ascorbic acid serum level well below the normal values of 0.4 to 1.5 mg. Purpura due to infections may be of either the thrombocytopenic or nonthrombocytopenic variety. Meningococcemia, severe streptococcal infections with purpura and the hemorrhagic rash of measles all have normal platelet counts.

Anaphylactoid, allergic or Schönlein-Henoch purpura has several identifying features. Detection of urticarial lesions which in a few hours become hemorrhagic is perhaps the most helpful if this happens to be one of the manifestations. Arthritic symptoms, usually involving the knees and ankles, occur in the Schönlein type, and abdominal pain, with or without bleeding from the intestine, is characteristic of Henoch's type. In addition there may be hematuria, albuminuria and casts which may make differentiation from acute glomerulonephritis difficult. Platelets are normal, and an eosinophilia may or may not be present. Protein hypersensitivity, often bacterial, and focal infections are considered to be the main etiologic possibilities. Identification and elimination of the offending allergen should be attempted, but success in this direction is apt to be limited. Cortisone or ACTH may be helpful in bringing an attack under control, but recurrences may take place for years.

Because of the danger of a complicating intracranial hemorrhage in any of the purpuras, efforts at controlling the bleeding should be as prompt and efficacious as possible.

LIMPING

A fifth symptom of sudden onset in infants and of frequent occurrence in the physician's practice, though of no great seriousness, but often baffling in etiology, is limping. This may be noted first when the child gets up in the morning or after rising from a nap, or it may occur at any time. As a rule the parents are unaware of any injury, there are no accompanying symptoms of illness, and fever is absent. Occasionally there may have been a recent upper respiratory infection. Most often the limping episode spontaneously disappears within a week or ten days. However, when the parents present the infant for examination, the physician cannot assume that this will be the course, and he is obligated to undertake a reasonable investigation in order to avoid overlooking significant pathologic conditions. Among the differential possibilities the following may be listed in order of likelihood: (1) toxic or traumatic synovitis; (2) soft tissue injury; (3) uncomfortable foot wear; (4) painful superficial lesions such as a paronychia of the big toe; (5) spinal cord lesion such as poliomyelitis; (6) fracture of a bone; (7) rheumatoid arthritis; (8) tuberculous hip disease; (9) septic arthritis; and (10) bone tumor or cyst. Rheumatic fever, aseptic necrosis and true flat foot would need to be considered in an older age period, but are unlikely in infancy. Scurvy and rickets should not be unilateral.

Toxic synovitis is suggested when there is a history of a preceding respiratory infection and when definite limitation of motion in one of the joints of the affected limb can be demonstrated. Synovitis due to trauma could hardly be distinguished from toxic synovitis unless there was a history of trauma. In my experience the hip is more often involved than are the ankle or knee joints. If the joints are free, careful palpation should be made of the soft tissues, searching for a tender area. Rarely, an imbedded foreign body such as a broken-off needle might account for the symptoms. Foot wear should be inspected for proper fit. Either shoes or stockings may be too short. Shoes may have nails protruding through the sole or have a wrinkled lining. A history of new shoes being worn for only a few days previous to the onset of the limping would offer a reasonable explanation. On one occasion I found a stocking tucked in the toe of one of the shoes. The limping promptly disappeared with its removal. Painful lesions of the skin such as a paronychia about a toe require no comment.

Poliomyelitis as a cause of the type of limping under discussion is a remote possibility. Usually the onset of the limping would be preceded

by a febrile episode. It is conceivable, of course, that this could have been overlooked by parents. Diminution of the knee jerk in the affected limb compared to that in the other member would suggest the possibility of a lower motor neuron lesion. If muscle weakness can be demonstrated and if any stiffness of the posterior muscles of the neck, back or hamstrings is present, a spinal puncture is indicated.

At this point further differential diagnosis depends upon laboratory or x-ray findings. These include a white blood cell count and differential, sedimentation rate, tuberculin test, and a roentgenogram of the infant's leg and pelvis. In most instances all will be within normal limits. In one or two instances I have found a spiral fracture of the tibia, presumably caused by the infant twisting his leg between the bars of his crib. In contrast to rheumatic fever, rheumatoid arthritis may have its onset in infancy, and the joints of the ankle or knee could be the first involved. Tuberculosis of the hip would be excluded by a negative tuberculin test and by the roentgenogram. Septic arthritis could hardly be present without symptoms of illness such as fever, leukocytosis and an increased sedimentation rate. Tumors of the bone or a bone cyst require an x-ray film for their unequivocal exclusion.

Physicians will undoubtedly differ in their feelings about the need for this type of investigation in a limping infant who yields no positive findings at the initial examination. Many might consider it reasonable to observe the infant a few days before subjecting the family to the expense of laboratory tests and roentgenograms. With this point of view the author would have no quarrel.

SUDDEN DEATH

Finally, in this consideration of some of the causes for sudden illness in infants, brief reference may be made to the relatively rare occurrences in the physician's practice of infants dying suddenly and unexpectedly, or moribund when first seen and dying a few hours later. Formerly many of these deaths were ascribed to status thymicolymphaticus. In recent years, however, this diagnosis has been made with decreasing frequency, and at present has been abandoned entirely by many competent pathologists. Arey, at the 1954 meeting of the American Academy of Pediatrics in Chicago, stated that an adequate cause of death could usually be demonstrated in a carefully performed autopsy by histologic, bacterial and biochemical studies. He reported his findings in 75 autopsies in clinically unexplained deaths. Two thirds of the deaths occurred in the first year of life, and half of these in the first six months. Thirty-four of the 75, or nearly 50 per cent, died from some type of infection such as sepsis, pneumonia and meningitis. Death may occur suddenly without prior progressive symptoms in bronchiolitis and bronchopneumonia.

Many young infants found dead in bed, supposedly from suffocation, actually die of pulmonary infection. Arey found no cases of suffocation in his series. There were three meningitis deaths and two from acute enteritis and enterococcal sepsis, presumably of viral origin. Ten of the patients died from congenital heart defects—three from fibroelastosis. Interstitial myocarditis accounted for some of the deaths. Four infants died from intestinal perforation secondary to volvulus or intussusception, and four died from poisoning.

This report of Arey's is in substantial agreement with similar studies made by others. It seems reasonable to conclude, therefore, that suffocation and status thymicolymphaticus are inadequate explanations for sudden deaths in infants.

SUMMARY

Six main presenting symptoms of sudden illness in infants commonly encountered by the physician in his pediatric practice have been discussed from the viewpoint of differential diagnosis, scope of investigation and, to a less extent, indicated therapy.

3200 University Avenue
Des Moines 11, Iowa

EDEMA IN INFANCY

B. M. KAGAN, M.D.

NATALIA S. FELIX, M.D.

PITTING EDEMA

The most common causes of pitting edema in the first two years of life are excess intake of minerals, whether given orally or parenterally, poor renal function, hypoproteinemia, hypogammaglobulinemia, sudden restoration of intracellular potassium with release of an excess of sodium which the kidneys cannot excrete, heart failure, and edema at the site of infusions. For less clear reasons edema occurs in infants born to diabetic mothers and in those with erythroblastosis fetalis. Rare causes in infancy are acute and chronic glomerulonephritis, nephrotic syndrome, beriberi and Milroy's disease.

EDEMA DUE TO EXCESS INTAKE OF MINERALS

Particularly in premature infants, an excess intake of minerals may lead to edema. The renal function of premature infants, especially with respect to sodium, is relatively poor. Cow's milk in many feeding mixtures contains approximately four and a half times as much mineral (usually measured as ash) as human milk. In general, as the percentage of calories from cow's milk protein is increased, there is also an increased intake of minerals. Because of the increased renal solute load thus presented and the existing renal insufficiency there is an increased tendency to edema.[30] This is reduced when the source of calories is in larger part from carbohydrate and fat, as in modifications of cow's milk in which

From the Kunstadter Laboratories for Pediatric Research and the Sarah Morris Hospital for Children, Michael Reese Hospital, Chicago.

Some of the original studies cited were made possible by grants-in-aid from the M & R Laboratories, Infants Aid and the Richard Slavin Memorial Club.

the proportions are similar to those in human milk. In such milks the mineral content is about two and a half times that of human milk. The trend in recent years to feed cow's milk without added carbohydrate to full term infants also results in an increased mineral intake and greater liability to edema, especially when illness increases the stress upon renal function above normal.[54]

In premature infants and in some full term and older infants whose renal function may be disturbed, the administration of an excess amount of salt along with fluids by parenteral routes may also result in edema.

EDEMA DUE TO IMPAIRED RENAL FUNCTION

Poor renal function due to such conditions as agenesis or cystic disease may be responsible for edema. Edema, however, is one of the less common manifestations unless a greater than usual amount of fluid with electrolyte is given.

EDEMA DUE TO HYPOPROTEINEMIA

The relationship between edema and hypoproteinemia (hypoalbuminemia) is well known. The infant with hypoproteinemia tends to edema when given fluids and electrolyte in amounts which ordinarily would not cause edema. In most instances hypoproteinemia and hypoalbuminemia are synonymous.[29] The usual causes of hypoproteinemia in infancy are as follows:[28, 31]

TABLE 3. *Causes of Hypoproteinemia in Infancy*

I. INADEQUATE SUPPLY OF PROTEIN
  A. Poor protein intake
  B. Intestinal malabsorption as in diarrhea, celiac syndrome, intestinal fistulas and so forth
II. DECREASED PROTEIN PRODUCTION as in liver disease, congenital hypogammaglobulinemia, and possibly with inadequate intake of vitamins, especially thiamine and ascorbic acid
III. INCREASED PROTEIN CATABOLISM?
IV. LOSS OF PROTEIN
  A. Via the
    1. Kidneys as in nephrosis
    2. Skin as in burns, weeping eczema or wounds
    3. Gastrointestinal tract as in persistent diarrhea
    4. Hemorrhage, acute or chronic
V. PROTEIN DILUTION as in excess fluid administration
VI. HEART FAILURE
VII. "IDIOPATHIC HYPOPROTEINEMIA" (cause not determined)

Moderate variations in maternal protein intake do not affect the serum proteins of the newborn markedly.[1, 16, 60] When the serum albumin concentration is diminished, it usually reflects severe depletion

of the reserves. If an infant is born with a normal amount of serum protein and thus presumably also of protein reserves, it may take weeks or months on a low protein intake before nutritional hypoalbuminemia develops. In later infancy the appearance of edema in protein starvation is well known in the form of "war" or "famine edema" or "kwashiorkor." The albumin fraction rather than globulin is readily affected by dietary intake of protein.[7, 28] In severe malnutrition, however, the globulin, particularly the gamma globulin, may also be depressed.[35, 39, 41, 56]

Edema in the neonatal period is more common in premature than in full term infants. Most neonatal infants with edema have practically the same serum protein concentrations as nonedematous ones.[25, 60, 69] Nevertheless, the edema may disappear as the protein concentration increases. The absence of edema in most premature infants in spite of low serum protein concentrations may be due to their low capillary hydrostatic pressure. For whatever reason, one cannot be satisfied with hypoproteinemia as the sole explanation for edema in newborn infants unless the levels are below those normally seen in those without edema. It is probably most often due to a combination of factors such as increased intake of electrolyte, and decreased renal function in addition to the low serum protein concentration.

The total serum protein concentrations in apparently normal premature infants range from 5 to 6 gm. per 100 ml. at birth. During the first month they decrease to from 4.1 to 4.7 gm. (average 4.5). Infants of lower weight tend to have lower levels than those of higher weight. The levels may not begin to rise until after 60 to 70 days of age. The serum albumin concentrations in premature infants range between 3.2 and 4.6 gm. per 100 ml. (average 4.0). The average then falls to about 3 gm. at 30 days of age.[31]

Hypoproteinemia may occur when absorption is impaired, as in chronic diarrhea, celiac disease and infrequently in fibrocystic disease of the pancreas ("eccrinosis").[27] It may also be seen when the liver for a variety of reasons fails to produce albumin.[28, 31]

Such conditions as weeping eczema and burns may result in loss of albumin through the skin sufficient to cause severe hypoalbuminemia and edema. Edema and related difficulty in regulating fluid balance in such conditions are common.

EDEMA DUE TO HYPOGAMMAGLOBULINEMIA

Congenital hypogammaglobulinemia[31] is an infrequent condition characteristically associated with edema. Edema may be so extensive that the patients look as though they have nephrosis. However, the blood cholesterol is normal or only slightly elevated, and they have no proteinuria. It appears to be due to a failure in formation of gamma

globulin and is associated with moderate lowering of the albumin concentration as well. It may be familial. In a number of instances a defect in the liver has been demonstrated. These patients are generally remarkably free from infection even though the gamma globulin concentrations are very low, although not absent. They tend to have low to low-normal total globulin concentrations (about 1.1 to 1.6 gm. per 100 ml.) and moderate lowering of the albumin concentrations (to about 2.3 to 3.3 gm. per 100 ml.). These cases should not be confused with another clinical entity referred to as agammaglobulinemia,[31] in which there is complete absence of gamma globulin probably due to hypoplasia of lymphoid tissue. In patients with agammaglobulinemia repeated infections are usual and edema not to be expected.

EDEMA DUE TO INTRACELLULAR POTASSIUM AND SODIUM EXCHANGE

When dehydration occurs during infancy, potassium is often lost from the cells and at the same time sodium enters the intracellular spaces. When there is a sudden reversal of this process by the administration of potassium, sodium may be released from the cells in large amounts. If renal function cannot handle this sudden increase in extracellular sodium, or if the serum protein concentration is low or cardiac compensation is inadequate to handle the increased volume of circulating fluid, edema may result.

EDEMA DUE TO HEART FAILURE

Edema caused by heart failure during infancy is the consequence mostly of congenital heart disease. Not infrequently an infant with congenital heart disease manages to get along fairly satisfactorily until an infection places so great a burden on the heart that it decompensates. As a result of the increased venous pressure and increased blood volume, together with slight lowering of serum albumin and decreased renal sodium clearance, edema of the pitting type appears in the lower extremities or the back. Heart failure may also result when an infant with a low serum potassium concentration receives replacement fluids containing an inadequate amount of potassium. In such cases the edema may erroneously be thought to be due directly to the administration of saline solution.

EDEMA AT INFUSION SITES

Edema at the site of infusion is not uncommon. It may be seen particularly when the venous return is impaired either by the mere pressure of the infused fluids or by a lesion in the vascular system. Edema

at the site of subcutaneous infusion may also result when the serum protein concentration is low or when an excess amount of salt has been given with the infusion. If the concentration of glucose used in the subcutaneous fluid is 5 per cent or greater, one of the early tendencies is for an increase in the amount of subcutaneous fluid and persistence of the edema for a longer time than otherwise. The use of hyaluronidase with parenteral fluids may result in the persistence or appearance of edema at other locations as well as at the site of infusion.

EDEMA DUE TO HORMONE ADMINISTRATION

As in older persons, excess or prolonged administration of desoxycorticosterone, adrenocorticotropic hormone or cortisone may result in salt and water retention with associated pitting edema.

EDEMA IN INFANTS OF DIABETIC MOTHERS

The edema of infants born to diabetic mothers contributes to the excessive birth weight which is a common characteristic.[33, 66] This may also occur in children of prediabetic mothers, that is, mothers who were nondiabetic at the time of delivery, but acquire diabetes later on—five, ten or even 20 years later.[2, 43–46] The cause may be some unknown disturbance of hormone function in the mother which begins before diabetes is clinically manifest.[13, 65]

Many explanations for the edema in infants born to diabetic or prediabetic parents have been offered. It may be a manifestation of vascular and hemodynamic changes[18] which are perhaps gene-linked with diabetes and of mesenchymal origin.[67] The vascular changes may be related to increased "sludging of blood"[52, 63] or to increased secretion of growth hormone by the pituitary.[5, 10]

It has also been suggested that intrauterine hypoxia may be responsible.[47] The cause of the intrauterine hypoxia is not known. The reason why it should result in edema is also not clear. The clinical and pathologic findings are similar to those observed in hemolytic disease of the newborn,[47] a disease which in severe cases is accompanied by intrauterine hypoxia. Both conditions are often accompanied by a general hydrops. The abnormal increase in number of nucleated red cells in the blood of infants of diabetic mothers is the consequence of increased erythropoiesis. This in turn is assumed to be caused by an attempt of the fetus to raise its oxygen-carrying capacity.

EDEMA DUE TO ERYTHROBLASTOSIS FETALIS

In erythroblastosis fetalis, edema appearing at birth is a bad prognostic sign. Most infants born with hydrops neonatorum die. A few,

however, who have mild edema at birth or exhibit it within a few hours of birth recover. The edema tends to disappear in these cases in two or three days if they live. The exact mechanism of the edema is not known. It may be due to increased capillary permeability caused by anoxemia in utero,[68] to capillary damage due to the antigen-antibody reaction,[70] to capillary damage caused by hemolysis,[34] to hypoproteinemia per se[26] or to a combination of both capillary damage and hypoproteinemia.[17] In the majority the serum protein levels are not sufficiently depressed to be the only cause of the edema.[53]

Some infants are born with "hydrops neonatorum," but have no evidence of erythroblastosis fetalis. Potter[52a] reported 17 such infants. They often have, in addition, marked hypoplasia of the lungs and spleen. One twin may have the condition, though the other is normal.

EDEMA DUE TO OTHER CAUSES

Edema of the *scrotum* or *vulva* is not uncommon and may be due to transmission of estrogenic substances from the mother. It is seen mostly in premature infants, and occasionally it extends over the abdomen and thighs. It may appear at any time in the first month or two of life. It usually disappears in a few days, but may last as long as one or two months. The general condition of the infant is good; otherwise the edema might be mistaken for sclerema or erysipelas.

Thrombosis of the venous trunks may cause edema of the *legs*. Fulminating acute infections, toxic states, severe anoxia, insufficiency of some of the endocrine glands (e.g., the thyroid and adrenal cortex), chronic anemia and severe malnutrition (even without severe hypoproteinemia) predispose to the development of edema. Most of these conditions appear to do so largely because they impair the restraining function of capillary walls. Decreased tissue elasticity may be a minor factor in debilitated infants. Occasionally generalized edema occurs without any explanation or discoverable cause.

Edematous swelling over the long bones of the legs may occur in scurvy. An even rarer cause of infantile edema today is early congenital syphilis. Such infants, in the experience of one of the authors (BK), have hypoalbuminemia which is perhaps related to impaired liver function.

Beriberi

Infantile beriberi occurs principally in breast-fed infants whose mothers suffer from manifest or latent beriberi.[24] Beriberi may appear soon after birth. About 80 per cent of the cases during infancy occur during the first three months of life. It is rare after the fifth month.[64]

One of the authors (BK) saw one such fatal case in an eight months old infant whose mother kept the cow's milk feeding warm all day in a thermos container and fed no supplements. Apparently continuous exposure of the milk to heat destroyed the thiamine. It is characterized by mild aphonia with a characteristic "beriberi grunt,"[61] vomiting and edema which is generally slight to moderate in degree and appears chiefly in the face and extremities.[11] The infant has a pseudoplumpness, the weight increase being actually due to waterlogging of the tissues.[19] Right-sided cardiac hypertrophy and dilatation result in sudden death if treatment is not instituted promptly. The infants respond well to thiamine chloride given intravenously.

The edema of beriberi may be due to a specific effect of vitamin B_1, in the absence of which intracellular edema occurs; in some cases it results from cardiac failure or an increase in intracapillary pressure; in others it seems associated with a fall in the serum proteins.[6]

Milroy's Disease

Milroy's disease, a rare condition,[3, 48, 49, 51] is characterized by (1) its congenital and hereditary nature, (2) the limitation of edema in one or both lower extremities, (3) permanence of the edema, and (4) complete absence of constitutional symptoms.

Milroy's original report[48] was based on a study of six generations of a family of 97 persons, 22 of whom had the disease. All except one was born with the disease. The edema is firm, but pits on pressure. It has a tendency to increase when the patient is upright and to subside to some extent with rest in bed. The edema is limited to one or both lower extremities, the area involved varying, but never extending above Poupart's ligament. It is neither painful nor tender and is without constitutional symptoms. It involves both sexes and is not inimical to long life.

Milroy speculated that the cause might be venous or lymphatic obstruction or an error in the nervous innervation of the blood vessels or lymphatics.

Many of the cases labeled Milroy's disease by others are probably examples of lymphedema praecox, some with a familial predilection.[3] These are not congenital or hereditary. They usually begin during adolescence, occur mostly in females, and worsen during pregnancy.

Glomerulonephritis and Nephrotic Syndrome

The common causes of edema in older children, that is, acute glomerulonephritis and the nephrotic syndrome, are rare in infants. The infrequency with which acute glomerulonephritis and nephrosis are found under two years of age can be seen in Figure 2. Nonsyphilitic

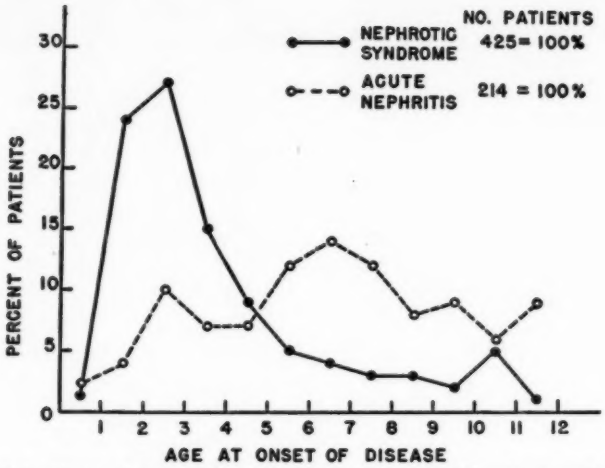


Fig. 2. Incidence of onset of the nephrotic syndrome in 425 patients and of acute nephritis in 214 patients at different ages. Data from The New York Hospital and from Barnett et al., Galan, and Heymann. (Reproduced with the kind permission of Dr. Barnett[4] and the publishers.)

acute glomerulonephritis has been reported in only five newborn infants.[14, 32, 37] The nephrotic syndrome is also rare in infancy,[20, 36, 40, 59] especially under one year of age.[38, 57] Chronic glomerulonephritis is also rare in newborn infants.[12, 50, 62]

NONPITTING EDEMA

Nonpitting edema in infancy is much less common than pitting edema. It may be due to allergy, angioneurotic edema, sclerema, pseudosclerema, the postacidotic state, tetany or infantile cortical hyperostosis.

Allergic edema in the form of urticaria is usually easy to recognize even though the etiologic factor may not always be easy to isolate.

In *sclerema* the edema is thought to be due to solidification of subcutaneous fat. It usually appears in the thighs, buttocks and/or lower back and extends down the legs until a large part of the body may become involved. Occasionally it is secondary to diarrhea. It is more common in the premature infant. In our experience, placing these infants in a heated incubator may reverse the progression.

Pseudosclerema may resemble sclerema, but is due to trauma with resultant hydrolysis or other change in the fat. Eventually it may result in calcification.

Angioneurotic edema is rare in infancy. However, it has been seen in the newborn and in the first few weeks of life.[8, 42] There is sudden de-

velopment of localized nonpitting, nonitching edema, sites of predilection being the eyelids, face, lips, extremities and mucous membranes of the tongue or genitalia and rarely the larynx. The genitals are a favorite site in the newborn. The duration is generally a few hours to a few days with a tendency to recur. It may be fatal when it affects the larynx, and tracheotomy may be necessary to save life. A hereditary tendency in the laryngeal forms has been reported.[9, 15, 23]

Edema is one of the manifestations of the "*postacidotic state*" which may follow diarrhea. It appears to be related primarily to hypocalcemia.[55] The edema is firm and generally resistant to pitting. It usually involves only the hands, feet and face, but occasionally is generalized. It is relieved within two or three days after calcium therapy. Its mechanism is obscure. The edema which may accompany manifest *tetany*,[21, 22, 58] also appears principally on the face, back of the hands, and dorsum of feet, but may be generalized.

In *infantile cortical hyperostosis* (Caffey's disease) there is often soft tissue swelling which usually does not pit. It appears most often over the mandible, clavicles, calvarium, scapulas and/or long bones.

Nonpitting edema, particularly of the feet and hands, which is usually symmetrical, has been described in a number of cases reported, especially from Europe and Great Britain, and called the "Bonnevie-Ullrich syndrome" or *pterygolymphangiectasia*. It is most common in females and often bears some resemblance to Turner's syndrome in that they may have congenital webbed necks, cubitus valgus and infantilism.[32a]

REFERENCES

1. Achard, C., Bariety, M., and Codounis, A.: L'équilibre proteique du sérum comparé dans le sang de la mère et le sang du cordon ombilical. Compt. rend. Soc. de biol., *102*:984, 1929.
2. Allen, E.: The Glycosurias of Pregnancy. Am. J. Obst. & Gynec., *38*:982, 1939.
3. Allen, E. V.: Lymphedema of the Extremities: Classification of 300 Cases of Lymphedema. Arch. Int. Med., *54*:606, 1934.
4. Barnett, H. L., Forman, C. W., and Lauson, H. D.: The Nephrotic Syndrome in Children. In Advances in Pediatrics. Chicago, Yearbook Publishers, Inc., 1952, Vol. 5, p. 94.
5. Berglund, G., and Zetterstrom, R.: Foetal Hypoxia in Maternal Diabetes. Acta Paediat., *43*:368, 1954.
6. British Encyclopedia of Medical Practice, Cumulative Supplement, 1951, p. 96.
7. Bruckman, F. S., D'Esopo, L. M., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration: Malnutrition and the Serum Proteins. J. Clin. Investigation, *8*:577, 1930.
8. Brunn, E.: The So-Called Angio-neurotic Edema. J. Allergy, *24*:97, 1953.
9. Bulmer, E.: Hereditary Angio-neurotic Oedema. Brit. M.J., *1*:766, 1929.
10. Campbell, J., Lei, H. F., and Davidson, T. W. F.: Production of Diabetes and Increased Erythrocyte Sedimentation Rate by Purified Growth Hormone. Endocrinology, *49*:635, 1951.
11. Chan, M.: Infantile Beri-beri in Kwangtung. Chinese M.J., *49*:676, 1935.

12. Collins, R. D.: Chronic Glomerulo-nephritis in a Newborn Child. Am. J. Dis. Child., 87:478, 1954.
13. Collis, W. R. F.: Diseases of the Newborn Baby: Babies of Diabetic Mothers. In Fanconi and Wallgren: Textbook of Pediatrics. New York, Grune & Stratton, 1952, Chap. V, pp. 259–260.
14. Conrad, C. E.: Urinary Findings in the Newborn, Report of Three Cases of Neonatal Nephritis. South. M.J., 31:636, 1938.
15. Crowder, J. R., and Crowder, T. R.: Five Generations of Angio-neurotic Edema. Arch. Int. Med., 20:840, 1917.
16. Darrow, D. C., and Cary, M. K.: The Serum Albumin and Globulin of Newborn, Premature and Normal Infants. J. Pediat., 3:573, 1933.
17. Davidsohn, I.: Fetal Erythroblastosis. J.A.M.A., 127:633, 1945.
18. Ditzel, J., White, P., and Duckers, J.: Changes in the Pattern of the Smaller Blood Vessels in the Bulbar Conjunctiva in Children of Diabetic Mothers. Diabetes, 3:99, 1954.
19. Earle, K. V.: Notes on Infantile Beri-beri in Nauru. J. Trop. Med. & Hyg., 44: 142, 1941.
20. Eiben, R. M., Kleinerman, J., and Cline, J. C.: Case Report of Nephrotic Syndrome in a Neonatal Premature Infant. J. Pediat., 44:195, 1954.
21. Falta: The Diseases of the Parathyroid Glands, in Endocrine Diseases. Philadelphia, P. Blakiston's Son, 1923, p. 194.
22. Feer: Edema of the Skin, in Diagnosis of Children's Disease. 2d ed. Philadelphia, J. B. Lippincott Company, 1928, p. 58.
23. Griffith, T. W.: Remarks on a Case of Hereditary Localized Oedema Proving Fatal by Laryngeal Obstruction. Brit. M.J., 1:1470, 1902.
24. Hawes, R. B.: Vitamin B-1 Deficiency. Brit. M.J., 1:414, 1938.
25. Hickmans, E. M., Finch, E., and Tonks, E.: Plasma Protein Values in Infants. Arch. Dis. Childhood, 18:96, 1943.
26. Jacobi, M., Litvak, A., and Gruber, S. J.: The Influence of Human Serum Albumin on Edema in Erythroblastosis Fetalis. J. Pediat., 29:177, 1946.
27. Kagan, B. M.: Cystic Fibrosis of the Pancreas, "Eccrinosis." Illinois State M.J., to be published.
28. Kagan, B. M.: The Clinical Significance of the Serum Proteins. South. M.J., 36: 234, 1943.
29. Kagan, B. M.: Studies on the Clinical Significance of the Serum Proteins: Relationship between the A:G Ratio, Albumin, Globulin and Total Proteins. Arch. Int. Med., 71:157, 1943.
30. Kagan, B. M., and others: Feeding Premature Infants—A Comparison of Various Milks. Pediatrics, to be published.
31. Kagan, B. M., and Stern, J. R.: Blood Protein Measurements in Diagnosis of Disease. P. Clin. North America, 2:265, 1955.
32. Karsner, H. T.: Congenital Nephritis. New York M.J., 88:1076, 1908.
32a. Keay, A. J., and Lewis, I. C.: The Bonnevie-Ullrich Syndrome. Arch. Dis. Childhood, 29:424, 1954.
33. Koller, O.: Diabetes and Pregnancy. Acta Obst. et Gynec. Scand., 32:80, 1953.
34. Kordenat, R., and Smithies, F.: The Phenomena Concerned with Reactions Following Transfusion of Blood; Clinical and Experimental Observations. J.A.M.A., 85:1193, 1925.
35. Krebs, E. G.: Depression of Gamma Globulin in Hypoproteinemia Due to Malnutrition. J. Lab. & Clin. Med., 31:85, 1946.
36. Kunstadter, R. H., and Rosenblum, L.: Nephrotic Glomerulonephritis and Nephrotic Syndrome in a 1,320-Gm. Prematurely Born Infant. Am. J. Dis. Child., 88:611, 1954.
37. Lapage, C. P.: Case of Hemorrhagic Nephritis in a Newborn Baby. Arch. Dis. Childhood, 6:235, 1932.
38. Leenhardt, E., Chaptal, J., Dufoix, M., and Monneer, P.: Nephrose lipoidique chez un nourrisson de onze mois: Evolution fatal sans hyperureoemie. Bull. Soc. de Pediat. de Paris, 29:412, 1932.

39. Ling, S. M.: Changes of Serum Proteins in Undernutrition. Chinese J. Physiology, 5:1, 1931.
40. Lyttle, J. D., and Goettsch, E.: Nephritis and Nephrosis. In McQuarrie, I. (ed.): Brennemann's Practice of Pediatrics, 1950, Vol. 3, Chap. 28, p. 14.
41. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization. Physiol. Rev., 20:194, 1940.
42. Menagh, F. R.: The Etiology and Results of Treatment in Angio-neurotic Edema and Urticaria. J.A.M.A., 90:668, 1928.
43. Miller, H. C.: Cardiac Hypertrophy and Extramedullary Erythropoiesis in Newborn Infants of Prediabetic Mothers. Am. J. M. Sc., 209:447, 1945.
44. Miller, H. C.: The Effect of Diabetic and Pre-diabetic Pregnancies on the Fetus and Newborn Infant. J. Pediat., 29:455, 1946.
45. Miller, H. C.: The Effect of the Prediabetic State on the Survival of the Fetus and the Birthweight of the Newborn Infant. New England J. Med., 233:376, 1945.
46. Miller, H. C., Hurwitz, D., and Kruder, K.: Fetal and Neonatal Mortality in Pregnancies Complicated by Diabetes Mellitus. J.A.M.A., 124:271, 1944.
47. Miller, H. C., Johnson, R. D., and Durlacher, S. H.: A Comparison of Newborn Infants with Erythroblastosis Fetalis with Those Born to Diabetic Mothers. J. Pediat., 24:603, 1944.
48. Milroy, W. F.: An Undescribed Variety of Hereditary Oedema. New York M.J., 56:506, 1892.
49. Milroy, W. F.: Chronic Hereditary Edema: Milroy's Disease. J.A.M.A., 91:1173, 1928.
50. Montagna, C. P., and Auspurg, G. Q.: Consideraciones sobre un caso de nefritis en un recien nacido. Am. Soc. Puericult. Buenos Aires, 8:257, 1942.
51. Notes and Reviews: Hereditary Oedema. J. Heredity, 23:323, 1932.
52. Odell, L., Aragon, G., and Pottinger, R.: Relationship between Erythrocyte Sedimentation Rate, Sludge Blood and Plasma Proteins during Pregnancies. Am. J. Obst. & Gynec., 54:596, 1947.
52a. Potter, E. L.: Universal Edema of the Fetus Unassociated with Erythroblastosis. Am. J. Obst. & Gynec., 46:130, 1943.
53. Potter, E. L.: Rh. Chicago, Yearbook Publishers, Inc., 1949.
54. Pratt, E. L., and Snyderman, S. E.: Renal Water Requirement of Infants Fed Evaporated Milk with and without Added Carbohydrate. Pediatrics, 11:65, 1953.
55. Rapoport, S., Dodd, K., Clark, M., and Syllm, I.: Post-Acidotic State of Infantile Diarrhea. Am. J. Dis. Child., 73:4, 1947.
56. Raynaud, M., and Laroche, C.: Etude sur le sérum des malades présentant des oedemes de famine. Compt. rend. Soc. de Biol., 137:216, 1943.
57. Saldun, M. L.: Nephrose lipoidique chez un enfant de onze mois. Arch. de med. enf., 36:41, 1933.
58. Shannon, W. R.: Generalized Edema in Association with Tetany of the Newborn. Arch. Pediat., 46:549, 1929.
59. Smith, C.: Personal communication citing one case of nephrotic syndrome in a newborn infant.
60. Smith, C. A.: Physiology of the Newborn Infant. 2d ed. Springfield, Ill., Charles C Thomas, 1950, p. 219.
61. Sodeman, W. A.: Pathologic Physiology: Mechanisms of Disease. Philadelphia, W. B. Saunders Company, 1950, p. 603.
62. Thompson, A. C.: Neonatal Glomerulo-nephritis. West Virginia M.J., 47:16, 1951.
63. Thorsen, G., and Hint, H.: Aggregation, Sedimentation Rate, and Intravascular Sludging of Erythrocytes. Acta Chir. Scandinavia, Suppl. 154, 1950.
64. Vedder, E. B.: Beri-beri and Epidemic Dropsy. In Oxford Medicine. New York, Oxford University Press, 1947, Vol. 4, Chap. X, pp. 298–301.
65. Warkany, J.: Etiology of Congenital Malformation. In Advances in Pediatrics. New York, Interscience Publishers, Inc., 1947, Vol. 2, p. 35.

66. White, P., and Hunt, H.: Pregnancy Complicating Diabetes. J. Clin. Investigation, 3:500, 1943.
67. White, P., and Waskow, E.: Clinical Pathology of Diabetes of Young Patients. South. M.J., *41*:561, 1948.
68. Wiener, A. S.: Pathogenesis of Erythroblastosis Fetalis: Statistical Evidence. J. Clin. Path., *16*:761, 1946.
69. Young, W. F., Hallum, J. L., and McCance, R. A.: Secretion of Urine by Premature Infants. Arch. Dis. Childhood, *16*:243, 1941.
70. Zollinger, H.: Pathologische Anatomie und Pathogenese des familiaren Morbus haemolyticus Neonatorum. Helvet. Paediat. Acta, *1*: Suppl. 2, 127, 1946.

29th Street and Ellis Avenue
Chicago 16, Illinois

THE INFANT WITH RESPIRATORY STRIDOR

PAUL H. HOLINGER, M.D.

KENNETH C. JOHNSTON, M.D.

Stridor is the term applied to the harsh, whistling respiratory sound resulting from obstruction of the upper air passages. Variation in the pitch of the stridor depends on the severity and position of the obstruction. A high-pitched stridor persisting throughout either inspiration or expiration signifies, in most instances, a severe glottic obstruction; a coarse, low-pitched, interrupted stridor is more commonly supraglottic in origin and indicates less severe obstruction; while stridor associated with a deep, barking cough is usually due to tracheal obstruction.

The respiratory phase of the stridor is significant. Inspiratory stridor alone, without an expiratory component, is more commonly due to supraglottic obstruction, although in some instances this is also seen in glottic and subglottic obstruction. Expiratory stridor alone is most commonly noticed in tracheal obstruction. Stridor which persists through inspiration and expiration may indicate glottic, subglottic or tracheal obstruction. Thus, while the phase of respiration during which the stridor occurs is not pathognomonic of the site of obstruction, nevertheless close observation of the character of the sound and careful timing of its relation to the respiratory cycle are of considerable importance in establishing the ultimate diagnosis.

An inspiratory stridor accompanied by changes in the voice or in the character of the cry, such as hoarseness, weakness or a change of pitch, suggests a lesion at the level of the glottis. Stridor accompanied by a muffled cry is characteristic of a supraglottic or pharyngeal lesion. A clear voice in association with severe stridor and severe dyspnea usually indicates subglottic or tracheal stenosis. Foreign bodies in the larynx,

or in the esophagus compressing the larynx, or lesions involving the glottis may cause severe inspiratory stridor and will be associated with severe impairment in phonation or even complete loss of voice. In the former instance this may be due to mechanical obstruction to approximation of the cords or to laryngeal edema, and in the latter by laryngeal or tracheal compression.

INSPIRATORY STRIDOR

Supraglottic Lesions

The supraglottic lesions commonly associated with inspiratory stridor include lingual and laryngeal cysts, acute epiglottitis, "congenital laryngeal stridor" (laryngomalacia) and supraglottic webs.

The stridorous infant with a (lingual) *thyroglossal duct cyst* at the base of the tongue usually exhibits increasing difficulty in feeding, and episodes of choking and gagging become frequent. The epiglottis is pressed backward and downward by the cyst, covering the larynx to produce the inspiratory stridor and a muffled cry. The lateral x-ray film of the neck for soft tissues outlines the cyst, showing the posterior projection of the rounded mass at the base of the tongue and the abnormal position of the epiglottis. Final diagnosis is made by palpation and by direct examination with the laryngoscope, depressing the tongue and bringing into view the shiny, midline, cystic mass. Needle aspiration of the cyst yields 2 to 3 cc. of thick, mucoid amber fluid, and the infant's symptoms subside instantly and completely. It may be necessary to aspirate the cyst several times during the first month after the diagnosis has been made, but the need for aspiration gradually diminishes and the cyst usually disappears by aspiration alone within a year.

The differential diagnosis of this lesion includes lingual thyroid and dermoid cysts, which may appear in the same area and may cause the same symptoms, but differ in the direct appearance and do not yield the characteristic mucoid secretion on aspiration.

Laryngeal cysts in the infant may occur as simple thin-walled cysts rising from the ventricle, or they may have a deeper origin under the false cord or from within the aryepiglottic fold. They produce signs of increasing laryngeal obstruction, with inspiratory stridor, sternal and suprasternal retractions, but in addition they are accompanied by hoarseness and, in the case of the cysts of the aryepiglottic fold, by dysphagia with choking and gagging during each attempt at feeding. A lateral x-ray film of the neck may show the cystic swelling in the larynx, but the diagnosis is made by direct laryngoscopic examination. The thin-walled cysts in the ventricle may be punctured with forceps and the excess tissue removed to give complete recovery and little chance of

recurrence. The cysts of the false cords and aryepiglottic folds usually demand immediate needle aspiration of the contents, and frequent aspiration thereafter may be necessary to maintain an adequate airway.

Supraglottic webs at the level of the aryepiglottic folds or the false cords result in marked inspiratory stridor, a subdued cry, hoarseness and suprasternal and sternal retractions. The x-ray film of the neck will probably show no definite or diagnostic abnormality, and diagnosis rests with direct laryngoscopy alone. The web may be dilated with laryngeal dilators, but if the obstruction is moderately severe, a tracheotomy will in all probability have to precede the attempts at dilatation.

"*Congenital laryngeal stridor*" (laryngomalacia) is the commonest cause of inspiratory stridor not accompanied by evidence of expiratory obstruction. The obstruction is in the larynx, but the origin is immediately above the glottic level. The infant has a normal cry, but the inspiratory phase of respiration consists of a fluttering stridor, usually high-pitched, and accompanied by suprasternal and sternal retractions. Though swallowing is not actually obstructed, in many instances the difficulty with inspiration causes a corresponding difficulty in feeding; in extreme cases the respiratory rate becomes so rapid and the infant expends so much time and effort in breathing against obstruction that there is little time left for quiet nursing. Cyanotic episodes are rare, however, unless some of the formula is aspirated in an attempt at too rapid feeding. The history usually indicates that the stridor has been present since birth and increases in intensity to the age of three to six months. From six months to a year little change may be noticed, but thereafter the stridor gradually becomes less marked and generally disappears by the time the infant has reached one to one and a half years of age.

The tentative diagnosis of congenital laryngeal stridor can often be made by the study of the history and by noting the characteristic fluttering type of inspiratory sound. The interrupted character of the stridor is due to the intermittent obstruction of the laryngeal airway by the soft, curled epiglottis and the flaccid arytenoids alternately covering and uncovering the cords. Direct laryngoscopy establishes the final diagnosis of the condition: the cords can be seen to move normally, but the epiglottis and the arytenoids show the marked tendency to be drawn into the airway on inspiration, causing the inspiratory stridor.

Glottic Lesions

Lesions at the level of the glottis causing inspiratory stridor other than bilateral laryngeal nerve paralysis are invariably accompanied by some abnormality of the voice or the cry. These disorders may be due

to congenital anomalies, trauma, acute inflammatory swelling or neoplastic changes. The more common congenital anomalies encountered at the glottic level are the webs of the true cords.

Congenital laryngeal webs may vary in structure and extent from a thin membranous web extending across the aperture of the anterior aspects of the true cords, to a thick membrane involving three fourths of the glottis, or even a fusion of the tissues of the anterior commissure. The extensive webs result in a considerable diminution of the airway, causing an inspiratory stridor and a weak or even entirely absent cry. Occasionally, in severe cases, an expiratory stridor may also be noticed. The symptoms are present from birth, and the stridor is persistent in all positions and is unchanged whether awake or asleep. Final diagnosis is made by direct laryngoscopy. If the web is thin, it may be incised with relief of the respiratory obstruction, and simple dilatation with laryngeal bougies can be performed at intervals to maintain or even increase the airway and the function of the larynx. In severe obstruction tracheotomy may be necessary, especially if instrumentation appears to be hazardous and difficult.

Paralysis of both vocal cords will result in a marked inspiratory stridor, an aspirate cry and other signs of acute respiratory obstruction, such as suprasternal and substernal retractions, episodes of choking, and cyanosis particularly with the feedings. The stridor may be present at birth and apparent in all positions throughout wakefulness and sleeping and appears to become progressively more severe with each succeeding day of life. The cry is usually weak but clear in bilateral paralysis, but has a slightly hollow or breathy character in unilateral paralysis. Unilateral paralysis is often an associated finding in a birth injury, accompanying an Erb's palsy. It is also seen as a complication of congenital heart disease or a vascular anomaly, either of which may cause a dysfunction of the left recurrent laryngeal nerve as it descends into the chest and under the arch of the aorta. Bilateral paralysis is frequently associated with central nervous system lesions, congenital or acquired, such as cerebral agenesis, meningomyelocele, bulbar poliomyelitis, and the like.

Direct laryngoscopy verifies the diagnosis and, when obstruction is severe, should be followed by a tracheotomy. Occasionally, when the lesion has been due to trauma, movement of the cords is regained within six months to a year and the tube may be removed. In other instances the paralysis is permanent and the tracheotomy tube remains until after full growth of the larynx has been obtained, when corrective surgical procedures can be performed.

Unilateral vocal cord paralysis commonly causes an inspiratory stridor of a lower pitch than the bilateral paralysis and more often is not associated with signs of severe respiratory obstruction. However, it is often

associated with coughing and choking during feedings because of the aspiration of fluids through the partially paralyzed larynx. A tracheotomy is usually unnecessary if the opposite cord has maintained full function, but occasionally it will be indicated if the choking episodes are frequent or attacks of cyanosis recur.

Laryngeal edema due to trauma may cause stridor. It may occur as a result of efforts to catheterize the larynx in the newborn for aspiration of the trachea, or it may follow bronchoscopy in the infant when the tube used was large in proportion to the size of the larynx. Similarly, a long endotracheal anesthesia may be responsible for the development of sufficient edema to cause symptoms. A foreign body, such as a flake of bone or an open safety pin, may lodge in the anteroposterior plane of the larynx, and with pressure and irritation, edema of the cords will follow. Traumatic edema arising from the sources mentioned causes an inspiratory stridor of varying severity, depending on the extent of the edema. Suprasternal and substernal retractions accompany the stridor, and the cry will be hoarse and in most instances comparatively strong. Usually the edema from trauma reaches its peak in 12 to 48 hours, during which time a tracheotomy may be necessary if the signs of obstruction become too severe before there is evidence that the edema is beginning to subside. Foreign bodies in the larynx should be removed immediately and the infant observed closely after the procedure, especially during the critical period mentioned, because of the possible need of a tracheotomy.

Laryngeal edema due to infection is a common clinical entity associated with respiratory obstruction and inspiratory stridor. It is seen in the acute inflammatory lesions such as acute laryngitis, laryngotracheobronchitis and laryngeal diphtheria. As a rule, the percentage of acute, obstructing infections of the larynx requiring tracheotomy is greater in infants over one year of age than in those less than one year of age. Obstruction and stridor in infants below one year of age are more often due to congenital anomalies. Acute laryngitis may occur suddenly during an upper respiratory infection, and signs of acute obstruction may be urgent and alarming. A severe inspiratory stridor will be noted with a hoarse cry and a croupy cough. The local signs are similar to those of acute laryngotracheobronchitis except that in the latter the stridor is often expiratory as well as inspiratory. The onset is similar, however; in simple laryngitis the infant is more often not as acutely ill as he may be with acute laryngotracheitis. In the latter the toxicity is marked, the temperature is high, and the infant rapidly becomes fatigued with the efforts of respiration. Early administration of antibiotics and high humidity are important. Fluid balance must be maintained, and close observation is necessary to ascertain when the obstruction is sufficiently severe to demand a tracheotomy. A rising pulse, signs of fatigue, and cyanosis or pallor demand urgent relief by tracheotomy.

The rapid onset of inspiratory stridor associated with fever and evidence of general toxicity should raise the question of laryngeal diphtheria, especially in the nonimmunized infant. Throat cultures should be made routinely on each infant admitted with stridor and obstruction to insure that no case of diphtheria is overlooked and to allow passive immunization as early as possible in those not yet immunized.

Laryngismus stridulus is the term used for laryngeal spasm occurring in infants of poor general health and often associated with rickets. It is characterized by attacks of whooping spasms with severe, crowing inspiratory stridor, lasting only a few minutes and occurring almost always during sleep; the attack subsides spontaneously with reassurance, mild sedation and particularly by placing the infant in a warm, highly humidified room. Because rickets is rarely seen in modern pediatric practice, laryngismus stridulus is a clinical rarity, generally seen only in neglected infants. The immediate treatment of croup by tent and steam inhalations is important, but the fundamental treatment consists in improvement of the general health.

The most common *neoplasm of the larynx* of the infant is papilloma. In a previous publication the authors reported 12 cases under one year of age in a series of 109 patients. The usual site of the lesion is at the glottic level, and the prominent symptoms are hoarseness followed by an increasing inspiratory stridor. If untreated, the obstruction can increase to alarming severity, and the stridor will assume an expiratory as well as inspiratory phase. Careful removal of the neoplastic tissue is indicated, using cup forceps under general anesthesia.

Subglottic Lesions

Hemangiomas and *lymphangiomas* occasionally involve the true vocal cords or the subglottic space. An inspiratory stridor will be noted, gradually increasing in severity as the glottic obstruction becomes more pronounced; in almost every instance a tracheotomy will be necessary before definitive treatment can be instituted. Direct laryngoscopy is indicated to visualize the lesion, but in this instance histologic proof is preferably obtained from lesions elsewhere if such are available rather than biopsy of the laryngeal tumor. Obstruction in the subglottic region by such lesions will usually cause both inspiratory and expiratory stridor. Suprasternal and substernal retractions will be present, and the severity of the retractions will vary in proportion to the obstruction. The cry is normal or may be weakened if the airway is markedly diminished.

Congenital subglottic stenosis is the commonest lesion in the subglottic area responsible for stridor. This consists in an infiltration of the subglottic tissues in the conus elasticus which, because of the constricting cartilaginous cricoid ring, produces marked obstruction with

even a minimal degree of involvement. It may be intensified by a distortion or maldevelopment of the cricoid cartilage, and in extreme cases of cricoid deformity the stridor may be so severe at birth that a tracheotomy must be done within the first few hours of life or asphyxia will occur. A recurrent or chronic subglottic edema of inflammatory or allergic origin will have the same signs and symptoms, but will not be persistent and probably will not have been present since birth. Direct laryngoscopy and bronchoscopy will reveal the true nature of the obstruction, and from this examination the question of tracheotomy can be answered. The operation is frequently necessary in those infants in whom the obstruction is moderate or severe, and the tube may have to be worn until the age of one to two years.

EXPIRATORY STRIDOR

Expiratory stridor alone is the outstanding symptom in tracheal lesions such as tracheomalacia, tracheal stenosis, extratracheal compression or tracheal tumors in the early or less severe phase of the obstruction. The trachea expands in inspiration and contracts on expiration; consequently the less severe obstruction will be noticed only on expiration. As the narrowing of the lumen increases, an inspiratory stridor will be apparent as well, resulting in a two-way stridor, the expiratory phase of which will be more pronounced. In tracheal lesions the expiratory stridor is usually accompanied by a croupy cough. On bronchoscopic examination the airway is seen to expand on inspiration, but a marked anteroposterior collapse will be noted on expiration, most pronounced just above the carina. Passage of the bronchoscope as far as the carina temporarily eliminates the stridor caused by a tracheal lesion.

Tracheal Lesions

Tracheomalacia is a relatively rare condition when not caused by an associated developmental tracheal compression. It consists in an absence of tracheal cartilages or a loss of their normal rigidity. It may cause stridor and obstruction severe enough to necessitate a tracheotomy, but more often no treatment is necessary and the condition disappears spontaneously between the ages of one and two years. When a tracheotomy does become necessary, the tracheotomy tube supports the walls, keeping the lumen patent.

A *congenital stenosis of the trachea* is a more serious condition. The stridor is two-way in type, and the voice is weak. A lateral film of the chest will show the narrowing of the trachea, and bronchoscopic examination reveals the narrow lumen with no change during the phases of the respiratory cycle. Tracheotomy may be indicated if the lesion is in

the upper trachea; if the stenosis is severe and in the lower trachea, the prognosis is unfavorable, since a tube long enough to pass through the stenotic area rests on the carina and the subsequent ulceration and granulation tissues obstruct the tube.

A *congenital tracheal cyst* will give rise first to an expiratory stridor and later to a two-way stridor as the cyst increases in size. Anteroposterior and lateral chest roentgenograms, fluoroscopic studies, films of the esophagus and bronchoscopic findings may be similar to those seen in vascular anomalies with tracheal compression. Exploratory operation is indicated.

Vascular anomalies with tracheal compression and particularly the vascular ring with tracheal and esophageal obstruction account for a considerable number of cases of two-way stridor in infants. As in the instances of tracheal obstruction mentioned before, the earliest signs may be an expiratory stridor, present since birth and possibly increasing and becoming both inspiratory and expiratory. Episodes of cyanosis and choking are commonly associated, and when a tight ring is present, the infant may have difficulty in swallowing and regurgitation. A barium swallow and anteroposterior and lateral chest films are indicated. The presence of a vascular ring is shown by the "cookie bite" defect in the right or left posterior aspect of the esophageal barium shadow just above the level of the tracheal bifurcation. Bronchoscopically, the trachea is seen compressed in the anteroposterior diameter above the carina, during both the inspiratory and expiratory phases. Surgical intervention is indicated when the diagnosis is made and the continuity of the ring severed either in its anterior or posterior component. The configuration of the trachea will usually not return completely to normal, but with the removal of pressure the symptoms are relieved. Most of the stridor disappears immediately after a successful operation, and the residue which may persist during effort and crying ultimately disappears entirely.

CONCLUSION

Stridor in infants indicates pharyngeal, laryngeal or tracheal disease or lesions causing pressure on these structures. The condition may or may not be serious, but the cause of the stridor should be determined. Critical evaluation of the history and clinical study of the type and phase of the stridor will suggest a tentative diagnosis, but radiologic, laryngoscopic, bronchoscopic or esophagoscopic examination must be made to provide the final estimate of the true nature of the lesion. In the inflammatory processes and in trauma the stridor is characterized by an acute onset. In congenital lesions the history generally indicates that symptoms have been present since birth. Stridor during the first

months of life is most often due to a congenitally soft, flaccid larynx, although congenital cysts, webs, paralyses of the larynx, and congenital vascular anomalies compressing the trachea will give similar signs and symptoms. Since the latter are often serious, an accurate differential diagnosis is imperative.

700 North Michigan Avenue
Chicago 11, Illinois

FREQUENT COLDS IN THE YOUNG CHILD

JEROME GLASER, M.D.

It is not a matter of common knowledge among physicians, including pediatricians, that the child with a frequently recurring or even apparently "continuous" upper respiratory infection or "cold" in most instances suffers from allergic nasal mucous membranes. This is not to say that there are no other causes for this condition, as will be discussed subsequently.

RECURRENT UPPER RESPIRATORY INFECTION

The recurrent upper respiratory disorder or infection involving allergic nasal mucous membranes, hereinafter designated as the RURI, is one of the most important, least understood and consequently most neglected of the allergic disorders of infancy and childhood.

Incidence

In the series of 516 consecutive allergic children studied by MacKinney and Glaser[12] the incidence of the RURI was 31 per cent, ranking second in the list of allergic diseases in infants and children ten years of age or less when first seen, asthma occupying first place with an incidence of 53 per cent. The RURI occurs about one third as often in adults, having been noted in 10 per cent of 200 successive adults seen in consultation and studied for the purpose of comparison.

Clein[4] apparently did not differentiate this disease from perennial allergic rhinitis in his report on the incidence of allergic disease in 100

From the Department of Pediatrics, University of Rochester School of Medicine and Dentistry, and the Pediatric Services of the Genesee and Strong Memorial Municipal Hospitals, Rochester, New York.

allergic children, and neither the RURI nor perennial allergic rhinitis is mentioned in the series of 250 allergic children reported by Ratner and associates.[17] The RURI was, also, not discussed in Chobot's[3a] textbook, nor is it described in Peshkin's[15] more recent monograph. This disease is nevertheless of great importance in pediatric practice, not only because it is a great nuisance, but also because it is a not uncommon precursor of bronchial asthma.

Differential Diagnosis

Probably the first to truly evaluate the importance of the RURI in infancy and childhood with respect to allergy were Cohen and Rudolph[5] in 1931. This disease must particularly be differentiated from the common cold and other forms of infection of the upper respiratory tract such as rhinitis, sinusitis, nasopharyngitis, laryngitis, tracheitis and bronchitis. Cohen and Rudolph pointed out that disorders of the upper respiratory tract in children may be divided into three classes, namely, (1) allergic, (2) infectious, and (3) combined allergic and infectious. The symptoms of all three are similar and are commonly associated with infections of the nose, nasopharynx, pharynx, and so forth.

Other conditions which in my experience may be responsible or often mistakenly blamed for the RURI are infected tonsils and adenoids. In this connection it is probably accurate to state that any child three years of age or less whose tonsils or adenoids or both are removed because they are suspected of causing recurrent "colds" is nearly always an allergic child.[8] The same is true of any child who has required removal of the tonsils or adenoids or both more than once. Organic defects, as a deviated nasal septum causing interference with sinus drainage, or chronic sinus infection or infection of recurrent lymphoid tissue in the nasopharynx following adenoidectomy with organisms highly resistant to treatment, and any organic cause of respiratory obstruction in the young infant may also simulate the RURI.

Among the more bizarre conditions associated with upper respiratory infections is Kartagener's triad of situs inversus, bronchiectasis and chronic sinusitis. Congenital heart disease, because of poor pulmonary circulation, is often accompanied by respiratory infection in the sense that any upper respiratory infection tends to invade the lower respiratory tract if the circulation is poor and the patient's resistance is low.* However, whether or not such patients are particularly susceptible to upper respiratory infections or whether or not the infection of the lower respiratory tract tends to spread to the upper respiratory tract has not been documented.

Recently there has been considerable discussion in the literature

* Personal communication from Dr. Helen B. Taussig.

concerning children with repeated infections because of agammaglobulinemia or hypogammaglobulinemia.[6b] Curiously, Janeway and his associates[10a] have also shown that children who suffer from chronic respiratory infections may have a hypergammaglobulinemia. In a group of four such children, several of whom had been previously suspected of suffering from agammaglobulinemia, the serum concentration of gamma globulin ranged from 1.9 to 4.5 gm. per 100 ml. as compared with normal values for the same age group of 0.6 to 0.9 gm. Though it is evident that much remains to be clarified in the relationship of gamma globulin to infection, a possible deficiency of gamma globulin should be considered in the child suffering from chronic, recurring upper respiratory infections, particularly if all other possible etiologic factors, including allergy, can be ruled out. If the recurring infections appear to be due to lack of gamma globulin, Janeway and associates[10b] recommend the injection of 0.1 gm. of pooled normal serum gamma globulin per kilogram of body weight every four to six weeks, and it appears to be necessary to reach blood levels of 0.10 to 0.15 gm. per 100 ml. in order for this to be effective. Dixon and his associates[6a] stated that in adults, whose gamma glubulin half-life may be less than that in children, treatments may be needed more frequently.

Cohen and Rudolph[6] published a summary of the differential diagnosis, reproduced in Table 4. This should be studied carefully. So thorough was their work that in the intervening years I have been able to add to their observations only the fact that the diagnosis of this disorder can almost always be made by the history alone. Usually the description of the chief complaint by the mother is sufficient to make the diagnosis in the great majority of cases. She commonly states, "Doctor, my child has one cold after another," and she may add, "all year long," or, "all winter long," or some other modification of a similar character. In contrast to this, in Rochester, New York, the average child has three colds a winter, usually one severe and two mild, lasting on an average of a week to ten days. Children having more colds than this must be suspected of suffering from the RURI of allergic origin or some other disease which has to be differentiated from this condition. Another point of minor significance is that with the RURI of allergic origin there is often a low grade fever as compared with somewhat higher temperatures which children occasionally manifest with an acute infectious coryza.

Often these children are brought to the physician's office in desperation. The child's tonsils and adenoids have been removed; he has taken vitamins to the point of saturation "to build up his resistance"; long hours and many months have been spent haunting the office of the nose and throat specialist for various types of intranasal treatment, lamp treatment, and the like, all to no avail. In all fairness to the nose and

TABLE 4. *Differential Diagnosis of Allergic and Infectious Conditions of the Upper Respiratory Tract in Children*[6]

ALLERGIC	INFECTIOUS
History	
1. Attacks usually recurrent	1. Attacks usually single
2. Often mild symptoms between attacks	2. Usually clears up completely
3. Definite relation to heredity	3. No relation to heredity
4. Not contagious	4. Contagious
5. Not related to exposure to another case	5. Definite relation to exposure to another case
6. Constitutional symptoms slight	6. Constitutional symptoms more marked
7. Foods and inhaled substances often traced as causes	7. No relation to foods or inhaled substances as cause
8. Itching common	8. No itching
9. Wheezing common	9. No wheezing
10. Other allergic conditions present or in past history	10. Usually no other allergic condition present or in past history
Examination	
1. Visible mucous membranes pale, glistening, edematous	1. Visible mucous membranes hyperemic, red
2. Thin, watery, mucoid nasal discharge; mucoid sputum	2. Mucopurulent or purulent nasal discharge and sputum
3. Smear shows eosinophils 10% or more	3. Smear shows polymorphonuclear neutrophils as predominant cells; eosinophils few or absent
4. Other signs of allergy often present	4. No other signs of allergy
5. Sinus involvement of hyperplastic type	5. Sinus involvement of purulent type
6. Wheezing breath sounds	6. No wheezing breath sounds
7. Roentgenogram shows bronchial markings increased	7. Bronchial markings not increased in roentgenogram
8. Allergic skin reactions usually positive	8. Allergic skin reactions usually negative
COMBINED ALLERGIC AND INFECTIOUS	
Primary allergic conditions are often secondarily infected. Cure depends on recognition and relief of the allergy. The body then overcomes the infection in most cases. This does not preclude treatment for the infection when indicated.	

throat specialists, however, it may be said that they are gradually coming to recognize this disease, and in Rochester, at least, many of these children are now referred to the allergist.

Diagnosis

The diagnosis of the RURI is confirmed by the finding of an eosinophilia in the nasal smear. For making satisfactory preparations the cotton swab should remain in continuous contact with the nasal mucous membrane for at least a minute.[7] Infants and young children will not

tolerate even for that short period the presence of tightly wound cotton, even when not attached to a wire or toothpick, without crying. The tears passing through the nasolacrimal duct into the nasal cavity may wash the cotton free from cells. However, on adapting the Bradford[2] postnasal flexible wire swab for this test, it is relatively simple to get good smears.

These swabs, which consist of a cotton tip thinly, tightly and evenly wound around one end of a strand of flexible wire, were originally devised by Bradford for taking postnasal cultures for detecting the presence of pertussis bacilli. When it is adapted for the purpose of demonstrating eosinophils, the child is held firmly on his back, the swab inserted until its tip rests against the vault of the pharynx, and the child then turned over onto the abdomen for a minute so that the tears will not flow back against the swab.

A less satisfactory method is to make the nasal smear in the usual manner by inserting tightly wound cotton swabs removed from an applicator or cotton on an applicator, as a toothpick, while closing the openings of the nasolacrimal ducts at the inner canthi of the eyes by pressure with the finger tips. The slide is then stained according to the method of Hansel.[9]

It is not necessary to demonstrate 10 per cent eosinophils as stated by Cohen and Rudolph.[6] If one can demonstrate in a nasal smear a definite increase of eosinophils over the usual 2 or 3 per cent which one learns by experience are found in control smears, that is sufficient. If an eosinophilia is demonstrated, regardless of other considerations, the burden of proof is upon the physician who states that the condition is not allergic. The absence of eosinophils, however, does not rule out the RURI of allergic origin. Hansel[10] has published illustrations in color depicting the various types of nasal smears which one may encounter.

PERENNIAL ALLERGIC RHINITIS

Occurring with almost identical frequency and often in association with the RURI is a condition now termed "perennial allergic rhinitis," although the older terms, "chronic nasal catarrah" and "vasomotor rhinitis" are more familiar. This disorder, which will hereinafter be designated by the initials "PAR," has also been termed "hyperfunctioning rhinitis" and "intumescent rhinitis." The disease is an important allergic condition of adults and occurred in 35 per cent of a series of 200 successive patients referred for consultation.[12]

The underlying pathology is a chronic, persistent allergic edema of the nasal mucous membranes. Most physicians do not differentiate PAR from the RURI, although they are different entities despite their close relationship, but include both under the term "chronic sinus-

itis." Just as in the case of the RURI, this disease has been sadly neglected by the pediatrician, who is in most instances not aware of its allergic origin.

Symptoms

PAR is often easily diagnosed by the history alone, and the same criteria as recorded in Table 4 are present. The mother will frequently state as the chief complaint, "My child has a cold all the time," or "I can't tell when he has a cold and when he doesn't," or "He never seems to be able to blow his nose." The chief symptoms, because of the nature of the underlying pathology, are sneezing or nasal discharge or obstruction, or any combination of these. Occasionally the nasal obstruction leads to a chief complaint of mouth breathing. The symptoms may be perennial without seasonal variation, although many children are worse during the so-called house dust season, a very apt term devised by Rinkel.[18] This starts when the weather begins to change in the fall and lasts until the heat is turned off when warm weather starts the following spring. In the same or other children, however, PAR may be complicated by "seasonal allergic rhinitis," i.e., the various forms of pollinosis as tree, grass (rose fever) and weed (hay fever). The symptoms of PAR are similar to those of pollinosis, though they are rarely as acute. The edema of the nasal mucous membranes in both the RURI and PAR predisposes to secondary infection, which occurs frequently in the RURI.

The chronic nasal congestion associated with PAR often causes the child to sniff and snort, a state of affairs which becomes very annoying to the parents, who insist that "if only he would blow his nose properly he would not have to make those noises." This, of course, is not true, because no matter how hard the child blows his nose he cannot blow out the congested mucous membranes which are causing the trouble, though the effort may occasionally cause epistaxis. The postnasal drip which may occur as a result of PAR may also induce the annoying habit of constantly "clearing the throat" or "hawking," in popular parlance. Much more serious is the development of a chronic intractable cough, usually worse at night, as a result of a postnasal drip or, more rarely, a persistent laryngitis. It is also occasionally observed in PAR that when the patient lies on one side, the dependent side of the nose will be obstructed by congestion, while the upper will clear. On changing position the obstruction will be reversed. This may lead to the child's constantly changing his position while in bed, the restlessness resulting in loss of sleep.

Bowen and Balyeat[1] described certain mannerisms (Fig. 3) characteristic of the child with nasal allergy. These are "nose wrinkling" and

"mouth wrinkling," which are due to an attempt to relieve itching of the nose due to nasal allergy. Another mannerism has been aptly termed by Bowen* the "allergic salute." This is done by the child's elevating the tip of the nose with the palm of the hand in an upward movement. It is altogether different from the common gesture used by the child to wipe off mucus from the nose. The child gives the "aller-

Fig. 3. *a* and *b*, Bowen's "allergic salute"; *c* and *d*, "nose wrinkling" and "mouth wrinkling." (Reproduced with the kind permission of Dr. Ralph Bowen.)

gic salute" or "Bowen's salute," as it is sometimes termed, because he has discovered by experience that this movement will somewhat relieve the nasal obstruction. The mechanism appears to be that the child with nasal allergy often has a watery secretion which spreads in a film from turbinate to septum. Pressure inward and upward on the tip of the nose tends to widen the intranasal space, separating the turbinates from the septum, thus breaking the film and promoting nasal aeration.

The RURI is at any age a not infrequent precursor of bronchial asthma; curiously, this appears to be less true with PAR. Since both are basically due to edema of the nasal mucous membranes, just as asthma is due for the most part to edema of the mucous membrane of the bronchi, these conditions might well be termed, for purposes of illustrating their significance to the patient, "asthma of the nose."

* This was first reported by Bowen at a meeting in Memphis, Tennessee, in 1928. Personal communication.

COMPLICATIONS

The complications of the RURI are essentially the same as those of any acute upper respiratory infection. Common complications of PAR in the adult are sinusitis, nasal polyposis and anosmia, the latter two fortunately rare in children, although perhaps children have anosmia, but do not complain about it. PAR in both the adult and the child may result in sinus infections because of edema of the membranes with defective drainage, usually ethmoiditis in the child. Hearing difficulty may occur in both the child and the adult because of chronic edema of the eustachian tubes, but fortunately this is not as frequent as might be expected.

One would expect almost a priori that long-continued nasal obstruction of allergic origin would result in maldevelopment of the face. It has been stated that failure of development of the sinuses, principally the maxillary and ethmoids (because the frontal sinuses are undeveloped in the young child), gives rise to the so-called allergic facies. Cohen[5] commented upon the frequency in allergic children of dental abnormalities associated with malformations and disturbances in growth of the dental arches and attributed this to interference by the allergic condition with the development of the facial bones. Straub,[20] in a study of 144 children under orthodontic treatment, found that about 40 per cent suffered from chronic nasal allergy, and in seven instances (17 per cent of cases) allergic gingivitis was also diagnosed. Straub agrees with those who urge the early diagnosis and treatment of nasal allergic conditions as an important method of reducing the incidence of dentofacial anomalies. Miller,[14] however, in a more recent study stated that he could find no evidence that allergy of the upper respiratory tract had any bearing on the production of dental arch deformities or occlusal relationships. This subject apparently needs further clarification, particularly because of other factors than allergy or infection which may influence sinus growth, as described by Rosenberger.[19]

TREATMENT

The specific treatment of the RURI and PAR is exactly the same as for bronchial asthma. In the RURI this is highly successful. PAR, on the contrary, is second among the allergic diseases only to the chronic urticaria of adults in the difficulty of obtaining satisfactory relief. Hypersensitivity to house dust, often clinically and nearly always by skin test, is usually present in both, more commonly in PAR, and hyposensitization to house dust and other inhalants is commonly necessary.

In some parts of the country it is also desirable to include mold extract in the treatment material. Commonly an autogenous or stock vaccine, or a mixture of both, appears to be helpful, although it is ex-

ceedingly difficult to evaluate bacterial vaccines in these conditions just as is the case in bronchial asthma. Concomitant pollinosis must also be adequately treated by the injection of the specific pollen extracts. In young infants and children, foods, especially cow's milk, are commonly important factors.

Tonsils and adenoids, if diseased, must be removed, and polyps and sinusitis of infectious origin as well as other organic diseases of the nose and throat treated as indicated. *None except emergency operative procedures should be carried out in the nose and throat during the seasons of grass and weed pollination,* because of the marked tendency of these children to pollen asthma after such operations.

In rare instances hypothyroidism may result in myxedema of the nasal mucous membranes with or without other evidence of hypothyroidism and produce the symptoms of PAR. I have studied one such case in a child and seen in consultation two adults with this disorder.

The symptomatic prophylactic treatment of the RURI will often produce highly satisfactory results *if properly carried out.* It is possible in most instances to abort the attack and, in those instances when the RURI is followed by asthma, to prevent or minimize the asthmatic attack. This is one of the most highly gratifying procedures in the armamentarium of the pediatric allergist. The routine which I have developed is as follows:

1. Bed rest
2. The simultaneous administration of the following medications for the first 24 hours and thereafter as necessary. They are given every four hours when the child is awake:
   a. An antihistamine
   b. A vasoconstricting nose drop
   c. A cough medication containing ephedrine or other similar sympathomimetic drug.

All these items are important, but perhaps the most important of all is to start as soon as possible after the first indication that the child is coming down with an RURI. In the great majority of cases this is indicated by undue sneezing or nasal discharge or cough or some other symptom such as lassitude or the general facial expression of the child. The mother can nearly always tell by long experience just what prodromata indicate an impending attack. In rare instances this may be a bizarre symptom, such as frequency of urination, which occurred in one of my patients. A delay of even an hour may mitigate against the best results.

The child's bedroom should be as free as possible from house dust, wool, feathers and pyrethrum-containing insecticides and from strong odors such as fresh paint, burning leaves, the dust from dried leaves, tobacco, tobacco smoke, cooking odors, perfume, kerosene, gasoline, moth balls, fresh cut flowers, and so on.

At present the routine use of antihistaminics for the prevention of colds has been largely discredited, as indicated by Burrage's[3] complete review. However, there may be a difference between using these drugs in allergic and nonallergic patients. Middleton and Rider[13] found that these drugs helped allergic as compared with nonallergic patients in a relatively small series. Though much further study needs to be done to clarify this point, there is no question whatsoever in my own mind regarding their great value if used as here described.

Before instillation of the nose drops the child should blow the mucus out of his nose if possible. If he is too young for this, the ingenious procedure devised by Landau,[11] which consists in using a soft rubber ear syringe with the tip trimmed to fit the nostril, is exceedingly useful for aspirating the mucus from the nasal passages of infants and young children.*

One of the most common errors in the administration of nose drops is failure to have the patient in the correct position, which was first described by Proetz.[16]

The child should be supine, with the head, supported by the mother, fully extended back over the edge of the bed so that the external auditory meatus and the point of the chin are in the same horizontal plane. Generally speaking, when the child is in this position, the nostrils will point directly upwards at the ceiling. The opening of the sphenoid sinus will then be at the most dependent portion of the nasal chamber, and the drops, after instillation, will not run backwards over the floor of the nose into the mouth, as they do when instilled in the usual manner, but will run downwards over the septum and turbinates to the roof of the pharynx, shrinking down the ostia of the various sinuses and promoting better drainage and ventilation. If the physician has any doubts regarding the great superiority of this method, he should try it himself when he has nasal congestion and be convinced.

The following cough mixtures have been highly satisfactory, and the one found by experience to be most effective for the particular child should be used. It is a practical point to number cough mixtures, as well as ointments and other medications, so that when the mother telephones or comes into the office, the preparation can be easily identified. The mixtures here described are for the average child five years of age. The doses of the various ingredients may be varied according to their effect upon the child and the age and weight of the child.

Label: Cough Mixture No. 1.	Codeine sulfate	0.25 gm. (4 grains)
	Ephedrine sulfate	0.40 gm. (6 grains)
	Glycerin	10.00 cc. (2 drams)
	Syrup hydriodic acid	
	Syrup of cherry, N.F., aa qs ad	120.00 cc. (4 ounces)

Sig: 1 tsp. every 3 to 4 hours as needed for cough.

If syrup of cherry is not available, as is sometimes the case in the smaller drug stores, soda fountain syrup of cherry, which is essentially

* A similar satisfactory apparatus with a glass nozzle is now marketed by the Becton, Dickenson Co.

the same thing, may be used in its place. The pharmacist should be given permission to do this on the prescription. I prefer this form of syrup of cherry to the more commonly used syrup of wild cherry (Syrupus Pruni Virginianae) because most children accept it more readily.

Another satisfactory cough medicine for a child of the same age is:

Label: Cough Mixture No. 2	Dihydrocodeinone bitartrate*	0.065 gm.	(1 grain)
	Ephedrine sulfate	0.400 gm.	(6 grains)
	Benylin expectorant† qs ad	120.0 cc.	(4 ounces)

Sig: ¾ to 1 tsp. every 3 to 4 hours as needed for cough.

If the foregoing measures fail to prevent or satisfactorily minimize an attack of an acute RURI, then, at the same time the antihistamine preparation, nose drops and cough medication are started at the onset of the next attack, an antibiotic should also be administered in large doses. It is uncommon for these measures to fail to give satisfactory and welcome relief. In the rare instances in which failure occurs when the attacks have been commonly followed by asthma, I have occasionally administered cortisone or corticotropin (ACTH) along with the antibiotic. This may be attended with some risk unless it is known that the organisms are sensitive to the antibiotic.

The symptomatic relief of PAR is a much more difficult matter. The antihistaminics will often relieve sneezing and nasal discharge but rarely nasal congestion. Nose drops rather than nasal sprays offer the best symptomatic relief. I commonly prescribe nose drops containing 1.5 per cent ephedrine or 0.25 per cent neosynephrine to be used on arising and before lunch and supper. I am not convinced that the addition of antihistaminics enhances the usefulness of such nose drops. At bed time Privine nose drops (Ciba), 0.05 per cent, may be used and also repeated once during the night if necessary. The patients are always cautioned never to use the Privine nose drops more than twice in 24 hours, and I have never observed sensitivity or nasal damage as a result of the use of Privine nose drops in this manner. The use of cortisone nose drops has been uniformly unsuccessful. It may well be that hydrocortisone nose drops or sprays will be developed which will prove exceedingly helpful. I have on rare occasions used oral cortisone in adults seen in consultation who could not otherwise be relieved, but have not yet used the steroids in children for this purpose.

* The adult dose is 5 mg. every four hours as necessary; children in proportion.

† This preparation (Parke, Davis and Company) contains 5 per cent alcohol and has a raspberry flavor. The active ingredients are:

Benadryl hydrochloride	0.08 gm.	(1¼ grains)
Ammonium chloride	0.8 gm.	(12 grains)
Sodium citrate	0.325 gm.	(5 grains)
Chloroform	0.12 gm.	(2 grains)
Menthol	0.006 gm.	(0.1 grain)

Occasionally when the nose is so completely obstructed by congestion that the drops will not penetrate, a hot bath will open the nasal passages sufficiently for this purpose.

SUMMARY

In summary, it may be stated that the frequently recurring or "continuous" cold of childhood is nearly always due to allergic nasal mucous membranes. These children may be divided into two groups. In one group the symptoms are for the most part intermittent and acute and resemble those of the common cold. This should be designated the recurrent upper respiratory disorder or infection of allergic origin (RURI). The second group of children suffers less acutely as a rule, but more continuously, from chronic allergic edema of the nasal mucous membranes, and this condition is presently termed "perennial allergic rhinitis" (PAR) in contrast to seasonal allergic rhinitis or pollinosis, although both conditions may coexist in the same patient. The diagnosis of both the RURI and PAR is made chiefly by the history and the appearance of the nasal mucous membranes and confirmed by the finding of an eosinophilia in the nasal smear.

Both the RURI and PAR should be thoroughly studied from the standpoint of allergy. House dust is one of the more important allergens in these diseases.

Both conditions can be treated satisfactorily from the symptomatic standpoint by antihistaminics, nose drops and cough medication. Occasionally an antibiotic is desirable if the problem of superimposed infection is involved. From the standpoint of specific therapy the RURI responds nicely, but PAR often only with great difficulty. It is important to study and treat these diseases not only for the purpose of alleviating the distress which they cause, but also particularly as prophylactic measures for bronchial asthma which may follow both, especially the RURI.

REFERENCES

1. Bowen, R., and Balyeat, R. M.: Facial and Dental Deformities Due to Perennial Nasal Allergy in Childhood. South. M.J., 27:933, 1934.
2. Bradford, W. L., and Slavin, B.: Nasopharyngeal Cultures in Pertussis. Proc. Soc. Exper. Biol. & Med., 43:590, 1940.
3. Burrage, W. S.: Antihistamines; Their Use and Abuse. New England J. Med., 245:532, 1951.

3a. Chobot, R.: Pediatric Allergy. New York, McGraw-Hill Book Company, Inc., 1951.

4. Clein, N. W.: The Growth and Development of Allergy. Ann. Allergy, 3:1, 1945.
5. Cohen, M. B.: Orthodontic Problems Associated with Allergy. Angle Orthodontist, 7:150, 1937.

6. Cohen, M. B., and Rudolph, J. A.: Allergic and Infectious Conditions of the Upper Respiratory Tract in Children. J.A.M.A., 97:980, 1931.
6a. Dixon, F. J., Talmage, D. W., Maurer, P. H., and Deichmiller, M.: Half-Life of Homologous Gamma Globulin (Antibody) in Several Species. J. Exper. Med., 96:313, 1952.
6b. Editorial: Agammaglobulinemia. J.A.M.A., 156:1084, 1954.
7. Glaser, J.: Differential Diagnosis of Bronchial Asthma in Infancy and Childhood. Ann. Allergy, 4:409, 1946.
8. Glaser, J.: Management of the Child with Chronic Asthma. Pediatrics, 3:96, 1949.
9. Hansel, F. K.: Clinical Allergy. St. Louis, C. V. Mosby Company, 1953, p. 411.
10. Hansel, F. K.: Op. cit., p. 414.
10a. Janeway, C. A., and others: Hypergammaglobulinemia Associated with Severe Recurrent and Chronic Nonspecific Infections. Am. J. Dis. Child., 88:388, 1954.
10b. Janeway, C. A., Apt, L., and Gitlin, D.: Agammaglobulinemia. Tr. A. Am. Physicians, 66:200, 1953.
11. Landau, D. B.: A Simple Mechanical Aid in the Treatment of Acute Rhinitis in Infancy. Am. J. Dis. Child., 60:635, 1940.
12. MacKinney, L. G., and Glaser, J.: The Incidence and Progression of Allergic Syndromes in Children. Presented at the 21st Annual meeting of the American Academy of Pediatrics, Chicago, 1952.
13. Middleton, J. W., and Rider, J. A.: Use of Antihistaminic Drugs in the Common Cold. Dis. of Chest, 16:879, 1949.
14. Miller, H. I.: The Relation of Long-Continued Respiratory Allergy to Occlusion. Am. J. Orthodont., 35:780, 1949.
15. Peshkin, M. M.: Allergy in Children. Progress in Allergy, 3:22, 1952.
16. Proetz, A. W.: Displacement Irrigation of the Nasal Sinuses. Arch. Otolaryng., 4:1, 1926.
17. Ratner, B., Collins-Williams, C., and Untracht, S.: Allergic Dermal-Respiratory Syndrome in Children. Am. J. Dis. Child., 82:666, 1951.
18. Rinkel, H. J.: Problems in Allergy. J. Missouri M.A., 46:81, 1949.
19. Rosenberger, H. C.: Does Sinus Infection Affect Sinus Growth? Laryngoscope, 55:62, 1945.
20. Straub, W. J.: Frequency of Allergy in Orthodontic Patients. J. Am. Dent. A., 31:334, 1944.

300 South Goodman Street
Rochester 7, New York

THE PALE CHILD

MILA PIERCE, M.D.

A consideration of the pale child seems to require an immediate definition of terms which will set the boundary of a discussion within a somewhat more limited field than the title suggests. There is a particular connotation to the word "pale" which brings "anemia" immediately into focus, but every pediatrician knows that the terms are not synonymous, unless one speaks of paleness of the skin, nail beds and lips. Pallor is a less specific term, suggesting lack of skin color, while pallid is perhaps the most descriptive of the three, connotating facial paleness due to fatigue, illness or emotional strain. The differential diagnosis presented by the sign of pallor in a young child requires a full scale appreciation of well and sick children throughout their period of growth, and to determine whether or not an anemia is present necessitates a knowledge of the normal blood values, and types of anemia common to childhood. In this discussion it is assumed that the reader is well informed on both counts, and that his interest in the subject of the pale child lies in a review of the etiologic factors, particularly those related to anemia.

PALLOR

Pallor is a common finding in the young child unless he is blessed with Titian complexion or the ruddy glow of a Nordic ancestry. All blond and many brunette children with fine-textured skin have a natural pallor which is not associated with anemia, although the anxious parent, who would be pleased to see a more colorful proof of the child's well-being, may be difficult to persuade that there is no need for a hematinic.

A pallid facies, on the other hand, presents a gamut of possibilities, not the least of which are environment and lack of out-of-door living. This "under-the-plank" paleness, common to all young plants in the spring, responds promptly to sunshine, and there is little or no evidence

that there is any direct relationship to the development of anemia. The tired child is pallid. The signs of chronic fatigue, which may originate in emotional strain, overstimulation or lack of adequate sleep, are found in the well privileged child as well as in his less fortunate playmates. The emotional factors which lead to anorexia, irritability, temper tantrum, inattention, diffidence or overactivity all need to be explored. However, although eating habits may be erratic, and emotional factors lead to capricious appetites, a severe nutritional anemia seldom develops after the age of three or four years unless there are other complicating circumstances such as recurrent infections. The pallid facies of the spastic child is more often the sign of fatigue resulting from great effort rather than of anemia.

On the other hand, the pallor which develops during the course of an obscure febrile illness may be indicative of a rapidly advancing anemia which is an integral feature of certain specific diseases—notably acute rheumatic fever, acute nephritis, malignant endocarditis, rheumatoid arthritis and the collagen diseases.

ANEMIAS

The degree of paleness in an anemic child is notoriously deceiving as an indicator of the grade of anemia, although the color of the pallor gives a clue as to the type. The lips and nail beds may remain pink until the hemoglobin level is less than 7 to 8 gm., although severe anemia is usually detectable clinically by transparency of the skin and paleness of the ocular and buccal membranes. The white pallor characteristic of acute or chronic blood loss, nutritional anemia and the "pure red cell" anemia provides a clinical sign which roughly separates the nonhemolytic group of anemias from those due to excessive blood destruction, in which yellow staining of the sclera and skin provides the characteristic subicteric or jaundiced coloring. In congenital hemolytic jaundice (spherocytosis), sickle cell anemia, thalassemia major and paroxysmal nocturnal hemoglobinuria the scleras are constantly icteric, although to a variable degree, being only a faint yellow during periods when hemolysis is not rapid and deepening rapidly during the periods of crises, when the blood bilirubin level is high. However, deep jaundice of the scleras in a child with any of these chronic hemolytic anemias should raise the question of homologous serum hepatitis.

Bronzing of the skin due to hemosiderosis develops in the chronic hemolytic anemias due to repeated blood transfusions, in the congenital hypoplastic anemias of the Fanconi type, and in nonhemolytic anemias due to a shortened life span of erythrocytes which requires a rapid turnover of the red cell mass. It is also seen in the hemophiliac, who bleeds into his own tissues, without excessive external blood loss. Conservative

use of transfusion therapy is highly desirable in all these chronic disorders to minimize the effect of hemosiderosis.

Symptoms

The symptomatology of anemia, per se, depends upon the acuteness and the type of anemia. Rapid blood loss from hemorrhage and a rapid blood destruction due to hemolysis produce the same train of symptoms—tachycardia, hypotension and circulatory embarrassment—but the hemolytic anemias place additional demands upon the renal clearance of hemoglobin and urobilin. The renal threshold is exceeded by a plasma level of 135 mg. per 100 ml. of free hemoglobin, and hemoglobinuria appears; once the threshold is broken, hemoglobinuria may persist until the level drops to 30 to 35 mg. Hemoglobinuria may occur in the acute hemolytic anemia of the Lederer type, but is rare in the crises of the chronic forms except for paroxysmal nocturnal hemoglobinuria; other causes are transfusion reactions, parasitic infection of red blood cells, and poisonings due to drugs (particularly sulfonamides), the favus bean and mushrooms. Urobilin appears in the urine in excessive amounts to produce the deep amber color during hemolytic crisis, and small amounts of bilirubin may also be present.

Symptoms common to the nutritional anemias—anorexia, fatigability and general apathy—are vague and nonspecific, and signs of circulatory embarrassment are lacking. There is little or no evidence that anemia per se contributes to retarded development, as the children with "pure red cell" anemia illustrate well. In the three cases I have followed up the children are alert and normal as to growth and development, at a hemoglobin level of less than 7 gm. throughout their lives. They have been remarkably free from the usual childhood diseases and respiratory infections in spite of the chronic anemia, and one cannot but speculate upon the protection given by the plasma factors provided by blood transfusions required to maintain their red cell volume at even a tolerable level. One is impressed also by the exercise tolerance which these children maintain with hemoglobin levels of 4 to 6 gm., and one is encouraged to avoid unnecessary transfusions to minimize the danger of iso-immunization and transfusion hemosiderosis.

Physical and Laboratory Examinations

Aside from the observation of color, an examination of the pale child should be directed particularly toward detection of hemorrhagic manifestations, signs of cardiac involvement, lymphadenopathy, and splenomegaly and hepatomegaly.

Blood Studies. The hematologic examination should include in-

formation regarding all the formed elements of the blood, and the concentration of hemoglobin in the red blood cells (see Fig. 4). Routine white blood cell and differential count by a competent observer who notes the appearance of the erythrocytes and platelets in the stained smear are primary essentials, both in excluding a primary blood disorder and in revealing the nature of the anemia. Standard equipment for photoelectric hemoglobin determination, accurate red blood cell count and microhematocrits are all that are necessary to determine the morphologic type of anemia—i.e., microcytic, normocytic or macrocytic, and

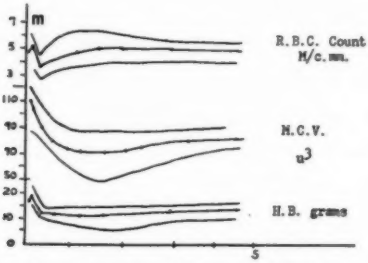


Fig. 4. Average range of erythrocyte and hemoglobin levels in children from birth to age 5 years. (George Guest: Nutritional Anemia. Robert Gould Research Foundation. 1947.)

hypochromic, normochromic or hyperchromic. It cannot be stressed too strongly that the pediatrician can be guided by the laboratory evidence of response to a specific hematinic, but he must direct the technician to the appropriate determination.

Bone Marrow Studies. The routine examination of the blood will be sufficient for the diagnosis and management of the large majority of the anemias in children, but examination of the marrow is indicated in the cases in which the diagnosis is obscure. It seems to me, however, that there are particular indications for diagnostic marrow examination and that the procedure can often be avoided by a careful study of the blood. In iron deficiency anemia the hypochromia and microcytosis are constant, and diagnostic, and a marrow examination is not necessary for diagnosis. On the other hand, megaloblastic anemia of infancy can be detected only by a marrow study; it can be suspected when a macrocytic normochromic anemia is found in a child under age two years. In the hemolytic anemias, particularly those with familial or racial backgrounds, a marrow study is not required for diagnosis, and will be required only if the etiology of the hemolytic anemia is obscure. If anemia is accompanied by hemorrhagic signs and a thrombocytopenia, a marrow examination is indicated to evaluate the origin of the thrombo-

cytopenia. However, puncture of the marrow should be avoided if a hemorrhagic tendency is present which is due to a defect in coagulation, as in hemophilia or hypoprothrombinemia, because of the danger of continued bleeding. Careful evaluation of the peripheral blood findings and bleeding and clotting times are necessary before a marrow biopsy is done.

Classification

In discussion of anemias common in infancy and children of different age groups, the following simple classification may be helpful.

TABLE 5. *Classification of Anemias of Childhood*

1. Anemia of blood loss
2. Nutritional anemias
3. Anemia of infection
4. Hypoplastic anemias
5. Hemolytic anemias

Neonatal Anemias

In the newborn, pallor accompanied by anemia, but without icterus, is indicative of (1) hemorrhage, internal or external, or (2) a primary aplasia of erythropoiesis.

Etiology. The most common causes of hemorrhage in the newborn period are asphyxia, birth trauma, bleeding from the cord, or a hemorrhagic diathesis. Asphyxia seldom causes massive bleeding, although petechiae are common, while intracranial hemorrhage, due to tears of the tentorium and subdural hemorrhage, will produce both pallor and anemia. Internal bleeding not due to birth trauma and severe enough to cause a significant anemia and pallor is usually accompanied by signs of cutaneous hemorrhage. In hemorrhagic disease of the newborn massive gastrointestinal bleeding may occur, usually accompanied by petechiae and purpuric bleeding into the skin; the hypoprothrombinemia of this disorder is detected by prolonged bleeding and prothrombin times. Thrombocytopenic purpura of the newborn will cause an anemia only if it is severe enough to produce visceral or gastrointestinal bleeding. The cases of congenital purpura occur more commonly in babies born of mothers with idiopathic thrombocytopenia than of normal mothers. It has been shown recently, however, that antiplatelet agglutinins[10] can be demonstrated in normal mothers who are sensitized to the infants' platelets. The transfer of the antiplatelet agglutinins across the placenta accounts for the thrombocytopenia in the infant in both instances. This type of neonatal thrombocytopenia is transient, but may

be severe while the antiplatelet antibody persists, and may require platelet-containing fractions of blood to control the bleeding tendency.

Aplastic Anemia. Primary aplastic anemia in the newborn occurs only in the "pure red cell" type of anemia. A transient aplasia may occur at age two to four weeks after the acute hemolytic cases of erythroblastosis fetalis, and is recognized by a sharp drop in the hemoglobin and erythrocytes and absence of reticulocytes. Recovery follows supportive transfusion.

Hemolytic Anemias. Icterus with pallor and anemia in the early newborn period is indicative of hemolytic disease of the newborn due to the passive transfer of maternal anti-Rh or anti-A or anti-B antibodies across the placenta. The diagnosis of *hemolytic disease of the newborn* is determined by (1) the detection of maternal Rh antibodies, (2) serologic evidence of placental transfer of antibodies to the infant, and (3) signs of blood destruction in the infant at birth manifested by anemia and jaundice which advances during the first few hours of life.

The evidence which has accumulated during the past two years by experience with large numbers of affected infants treated by exchange transfusions supports the contention that adequate treatment of this disease consists in removing the products of blood destruction from the infant's circulation as well as replacing new red blood cells. The infant who is severely affected at birth, whose cord blood hemoglobin is less than 13 gm., requires prompt exchange transfusion therapy, with repeated exchanges at intervals determined by the blood level of bilirubin and the clinical status of the infant. The critical level of hyperbilirubinemia varies with the age of the infant; levels above 6 mg. per 100 ml. at birth, 15 mg. at 12 hours and 20 mg. at 24 hours are excessive, and correlate well with other ominous signs of the disease. Not only has the mortality rate been lowered sharply by exchange transfusion therapy, but the incidence of neurologic damage due to kernicterus has been reduced significantly.[12]

Congenital familial hemolytic anemia (congenital spherocytosis) may present a picture similar to that of hemolytic disease in the newborn, and recently a new entity, *"congenital nonspherocytic hemolytic anemia"*[1] has been described in a newborn. In both these diseases the rate of blood destruction may be sufficiently rapid that a critical level of hyperbilirubinemia is present. Opinions differ[8] at present regarding the necessity for exchange transfusions in these congenital types of hemolytic anemias, although it would seem reasonable to argue in favor of exchange therapy if the crises in the neonatal period were severe enough to produce a significant anemia and critical hyperbilirubinemia in the first three days of life, particularly if ominous clinical signs suggestive of kernicterus developed.

Anemias of Infancy and Early Childhood

Anemias within the first three months of life may actually have their origin in the newborn period. Early clamping of the cord, which robs the infant of a full quota of placental blood volume, or any of the aforementioned mechanisms which lead to blood loss or destruction, exhaust the supply of fetal blood which tided the infant over the period of transition from fetal to adult hemoglobin synthesis. It has been shown[19] that the ratio of fetal hemoglobin to adult hemoglobin is low in hemolytic disease of the newborn; the rate of recovery from anemia after the loss of fetal blood is dependent upon the ability to synthesize adult hemoglobin. The percentage of reticulocytes is an indicator of the regenerative capacity of marrow, and a valuable guide for therapy at this age. Normally the reticulocyte count falls from 2 to 3 per cent in the neonatal period to 0.1 to 0.2 per cent by the eighth to twelfth week, when it rises again to 0.5 to 2.0 per cent. This fall and rise shifts to an earlier age period with the stress of blood loss. If the reticulocytes remain at a normal level or slightly elevated, erythropoiesis is active, and one may expect that the hemoglobin and erythrocyte level will rise to an adequate level without transfusion therapy. If, however, the hemoglobin is less than 7 gm. and the reticulocyte count is low, 0.1 to 0.05 per cent, transfusions may be required unless the case can be closely followed up. An infection which would further inhibit hemoglobin formation would lower the hemoglobin level rapidly at this point.

Iron Deficiency Anemia. Throughout infancy and the first three years of life, iron deficiency anemia is by far the most common anemia of childhood. In spite of advances in our knowledge of the nutritional requirements for iron, and the introduction of iron-containing foods at an early age, iron deficiency anemia continues to be seen in severe forms in young children in every pediatric clinic. It is, however, rare in older children except in the chronic diarrheal states or in the mentally defective child with an erratic appetite.

ETIOLOGY. Aside from the obvious etiologic factors concerned with lack of dietary iron, or failure to absorb it due to digestive disturbances, there are many unknown factors in the development of iron deficiency anemia. The thesis that iron depletion results from (1) inadequate store of iron in the fetal liver and (2) a failure to ingest sufficient dietary iron during (3) a period of rapid growth is an oversimplification of the evidence now at hand. There is some support to the claim that the hypoferremic state in the mother during pregnancy[20] contributes to anemia in the child, but there is little evidence that any "stores" of iron exist in the liver. It seems more likely, as Langley[15] suggests, that the high iron content of the liver at birth is determined by the hematopoietic tissue in the liver. Since the amount of iron per gram of liver

tissue is as high in the premature as in the full term infant, it cannot be said that an insufficiency of iron exists in the premature, although the supply would be exhausted sooner. In his scholarly review of iron metabolism and the hypochromic anemias, Josephs[13] points out again that growth is the critical factor. He suggests another interpretation for the role of growth, concluding that "growth produces an imbalance between the supply and demand" rather than a depletion of iron stores. Infection contributes to an iron deficiency by inhibiting erythropoiesis directly, and the plasma level of iron falls as well, as Cartwright[3] and his group have shown. These findings suggest that there may be a competitive demand for iron by different tissues.

TABLE 6. *Daily Iron Requirements*

AGE	MAINTENANCE	THERAPEUTIC DOSE	
	Normal Dietary Intake	Available Iron	Ferrous Compound
Infancy	2–8 mg.	15–45 mg.	1½–6 grains
Children:			
1–2 years	6–10 mg.	45–75 mg.	3–6 grains
2–12 years	10–12 mg.	90–120 mg.	6–12 grains
Adolescents:			
Boys	12 mg.	120–125 mg.	6–15 grains
Girls	15 mg.		

The mechanism for the removal of iron from the plasma and its delivery to the red cells (where it is incorporated into the porphyrin nucleus at the erythroblast-reticulocyte stages) is a subject of many investigations of extraordinary interest. Cartwright and his co-workers observed (1) a rise in plasma iron after blocking the reticuloendothelial cells with collargol and (2) a fall in the plasma iron after shock, infection, injection with epinephrine and ACTH. These findings suggest that there may be a regulatory mechanism for the movement of iron which is mediated by the adrenal cortex and the reticuloendothelial system, and that the balance which is maintained in the older person is disturbed during a period of rapid growth.

EFFECT OF TREATMENT. The characteristic blood picture of iron deficiency anemia is a hypochromic microcytic anemia with anisocytosis of the red blood cells and a low hematocrit. The leukocyte and platelet level are normal. The response to iron therapy is best followed by serial determination of hemoglobin, hematocrit and reticulocytes at weekly intervals. If the dosage of medicinal iron is adequate (Table 6), the first response is reticulocytosis within five to seven days, followed by a rise in the red blood cell count and hematocrit, and, lastly, by an in-

crease in hemoglobin level. When the blood values have returned to normal and the appetite for iron-containing foods has recovered, there is no further need for additional iron. There is little or no evidence that vitamin deficiency plays a significant role in iron deficiency anemias or that excessive vitamin supplements accelerate recovery.

Megaloblastic Anemia. The occurrence of megaloblastic anemia due to a deficiency in folic acid is less common than it was a few years ago, since the need for the addition of folic acid to synthetic milk preparations has been elucidated. Human and goat's milks contain less folic acid than cow's milk, and infants fed exclusively on breast milk or goat's milk are apt to exhibit the syndrome unless additional folic acid is added. May and his group[16] determined the need for ascorbic acid in the folic acid deficiency state. Megaloblastic anemia of infancy is a true deficiency anemia which results from an arrest in erythropoiesis in the megaloblast stage, but it is corrected by the administration of folic acid combined with adequate vitamin C.

Nutritional Anemias. In children over two and a half or three years of age nutritional anemias are rarely the cause of a severe anemia, but at this age a high grade anemia with a hemoglobin value in the range of 7 to 8 gm. or lower should lead one to suspect the primary disorder of the blood.

Leukemia. The incidence of leukemia is higher at the ages of three to six years than at any other age. The sudden onset of a white pallor associated with fever, a tendency to bruise, and lassitude are cardinal, although not pathognomonic, symptoms of this fatal disease. Although the leukocyte count varies considerably in the early course of leukemia, ranging from a hyperleukocytosis with a high percentage of blasts to a leukopenic level without detectable leukemic cells in the peripheral blood, some degree of anemia is uniformly present and is usually rapidly progressive and severe. The mechanism of anemia in the early leukemia process has not been explained satisfactorily, but it is clear that erythropoiesis, granulocytopoiesis and platelet production are suppressed, before the bone marrow is actually crowded with leukemic cells. This depletion of the normal cellular elements of the marrow can be demonstrated, though rarely, when the marrow examination is made in the early stages of the disease, and by repeated study of the marrow throughout the periods of relapse and remission while the child is under treatment with the newer chemotherapeutic drugs.

TREATMENT. At present there are three effective drugs for the control of acute leukemia: namely, the adrenocortical hormones, ACTH, Cortef and cortisone;[18] the antifolic acid drugs,[7] aminopterin and amethopterin; and the purine inhibitor 6-mercaptopurine.[2] We have been particularly impressed with the active erythroid regeneration which follows steroid hormone, and have used ACTH as our first therapeutic agent

of choice because of this prompt recovery of erythropoiesis and also because of the prompt disappearance of leukemic cells which can be obtained in a high percentage of children treated, about 75 per cent. It has been our experience that the requirement for transfusion is lessened by steroid therapy even if the addition of one of the chemotherapeutic agents is required to bring about sustained remission.

As leukemia progresses, however, an aplastic anemia develops and becomes a constant feature of the terminal stage of the disease. This aplastic type of anemia is recognized as an integral part of the leukemic process, although it is true that all the chemotherapeutic drugs currently used in the control of leukemia are depressant to all cells of hematopoietic tissues as well as inhibitors of leukemic cell proliferation. It is not uncommon for a hemolytic anemia to develop either in the early stages of the disease or later. This tendency to an acquired hemolytic anemia is not entirely explained by repeated transfusions, since it may be seen as one of the initial symptoms.

Aplastic Anemias. The *idiopathic* type of *aplastic anemia* may be extremely difficult to differentiate from the leukopenic phase of leukemia by clinical or hematologic examination, even in the hands of an experienced hematologist. When the onset is insidious and the pancytopenia is identical with the "aleukemic" leukemia, the diagnosis can be determined only by study of the marrow. Aspiration samples may be inadequate, and the biopsy specimens should be chosen to avoid cartilage. In aplastic anemia the distinctive feature is quantitative rather than qualitative as in leukemia; the total cellularity is reduced, the marrow appears to be stripped of normal myeloid elements, but still holds a few myeloblasts and small lymphocytes among the supporting reticular network of the marrow; the dense aggregates of blast forms common to even the aplastic phase of leukemia are absent. Although the prognosis is grave in these idiopathic types of aplastic anemia, it is not uniformly fatal, and several cases are now on record which have responded to steroid therapy with supportive transfusions.

Chronic aplastic anemias are more rare, but constitute an interesting group of cases in the pediatric literature, and one suspects that they are more common than the number of reported cases would indicate. Fanconi[6] described a familial type of aplastic anemia, associated with congenital defects of the skeleton, dwarfism, and bronzing of the skin, and there are now several such families on record.[21] Abnormalities of the urinary tract are not uncommon in these children, although they appear to be associated defects rather than related to the dwarfism which is part of the syndrome. The peripheral blood findings are those of a pancytopenia, but the marrow is usually hyperplastic rather than aplastic. No abnormality in the hemoglobin has been found, and there is no evidence of a hemolytic component in this disorder. Splenectomy

is usually ineffective, although some cases have been improved[5] without full recovery. The steroid hormones may also be ineffective, although I have followed up two patients who have shown marked improvement in the purpura and anemia on either ACTH or cortisone therapy.

The *"pure red cell" anemia* is a specific entity which differs from other forms of aplastic anemia in that it is the erythrocytic series alone which is depressed; the qualitative and quantitative values for leukocytes and platelets and their precursors are normal in the blood and marrow. There is a paucity of normal erythroid forms in the marrow, and reticulocytes are absent in the blood. This entity is often recognizable in the early weeks of life as an anemia of the newborn, without jaundice, when the blood findings are those of a severe normocytic and normochromic anemia, with a failure to obtain reticulocytosis after iron therapy or transfusions. The child is dependent upon transfusions for life, and it is imperative that type-specific blood be used at all times to avoid sensitization. The development of icterus indicates the development of a hemolytic component due to iso-immunization produced by previous transfusions; the Coombs test will then become positive as in acquired hemolytic anemias. With persistent and meticulous care throughout the repeated transfusion therapy these patients may eventually undergo a spontaneous recovery. The stimulating effect of the adrenocortical hormones has been demonstrated on these cases, but a sustained remission after withdrawal has not been reported, to my knowledge. The two patients we have followed up are now seven and eight years of age respectively, and have not yet had a spontaneous remission. Diamond[4] reported remission in three of 12 cases.

Hemolytic Anemias. In contrast to the white paleness of the nonhemolytic anemias, icterus of the skin and scleras is a constant feature of the hemolytic anemias of childhood. The staining of the skin due to carotenemia is readily excluded by an absence of yellow discoloration of the scleras. The characteristic blood findings, as in all hemolytic anemias, are a parallel reduction in hemoglobin and erythrocyte values, a reticulocytosis, increased excretion of urobilinogen in the stool, and a variable degree of hyperbilirubinemia.

The *acute hemolytic anemias* are self-limited as a rule and respond to supportive transfusion; however, the hemolytic process may continue for several weeks or months, developing then into a prolonged chronic type. The favorable effect of the adrenal cortical hormone on the acquired type of hemolytic anemias has been demonstrated repeatedly, both in the acute and the chronic forms. The mechanism of hemolysis in the acquired types of hemolytic anemia has been clarified by the demonstration of a hemagglutinin in some cases. The development of the Coombs test which reveals the presence of an antibody which has at-

tached itself to the red cell has helped to separate the hemolytic anemias due to antibody production from those due to other types of hemolysins. In the cases of hemolytic anemia that occur in certain viral infections such as infectious mononucleosis, hepatitis, viral pneumonia, it is questionable whether the hemolytic processes are actually due to a specific or heterospecific hemagglutinin or to the direct effect of the infected agent upon the surface of the red cells, which then alters the protein of the red cell stroma so that it becomes antigenic for the production of antibodies. This rather attractive hypothesis has not yet been satisfactorily demonstrated, but in the cases of acquired hemolytic anemia in which the Coombs test is negative it offers a reasonable explanation.

The *chronically pale child with a constitutional, hereditary, hemolytic anemia* has been the subject of intensive investigation which has yielded valuable information in the last few years regarding the mechanism of these various anemias. One by one the identification of the specific abnormality in the red cell which decreases its span of life is being recognized. The defective cell of congenital spherocytosis was described first by Haden[9] as a spheroid cell with decreased osmotic resistance, which explains its fragility in the blood stream. Herrick[11] described the sickle shape of the red cell in sickle cell anemia, but the defect which causes the sickling phenomenon has been explained by Pauling's[17] discovery of hemoglobin S, and has clarified the relationship of sickle cell trait to the active disease. Persons with the trait are heterozygous for the defect in hemoglobin synthesis, while the person with the active disease inherits the gene from both parents and is homozygous for the defect. Hemoglobin S forms elongated, crystalline structures within the erythrocyte under conditions of reduced oxygen tension, which distorts the cell to form the sickle-like shape, and causes rupture of the cell which leads to constant anemia and crises. In addition to hemoglobin S, two other abnormal hemoglobins[17] have been identified electrophoretically in Negroes, i.e., hemoglobin C and D, each of which is responsible for chronic hemolytic anemia in the homozygous state, and each of which causes mild anemia when matched in the heterozygous state with persons with hemoglobin S. The sickling phenomenon occurs in both hemoglobins, although hemoglobin C characteristically produces a large number of target cells.

In *thalassemia* major and minor the nature of the defect in synthesis of adult hemoglobin is not known, although the hereditary pattern is the same as in sickle cell disease. It is thought that the deficiency of adult form of hemoglobin is compensated for by the production of fetal hemoglobin which is present in large quantities in both the major and minor forms of this disorder. Cases have been reported of a milder form of hemolytic disease which results from intermarriage between persons who are heterozygous for hemoglobin C and for thalassemia minor. Be-

cause of the difference in the severity of these various forms of constitutional anemias, it is important to detect the specific difficulty, from a viewpoint of both prognosis and therapy.

TREATMENT. The treatment of these anemias is unsatisfactory except for congenital hemolytic icterus or spherocytosis, which is the only one of the chronic hemolytic anemias in which splenectomy brings about a prompt and lasting improvement. In sickle cell disease repeated transfusions are to be avoided in order to minimize the danger from isoimmunization and transfusion hemosiderosis. The pain of crisis may be alleviated by short-term courses of ACTH or cortisone and the need for transfusions avoided as well, although they are necessary at times, particularly during attacks of acute infection. The milder forms of anemia which result from combined hemoglobin C and S do not carry the severe prognosis that sickle cell disease does and may require no therapy. In thalassemia major the percentage of fetal hemoglobins drops after splenectomy, and the question is again reopened regarding the benefit obtained with this procedure in the severe cases in young children. In the cases reported to date in our own experience a retarding, but not an impressive beneficial effect has been noted.

SUMMARY

An appraisal of the sign of pallor requires a knowledge of the racial, hereditary and sociologic background of a child as urgently as a physical examination. From fetal life through childhood, maternal and hereditary factors play a primary role in determining the presence or absence of anemia in the child.

The placental transfer of maternal antibodies per the infant's red cells and platelets produces the clinical entities of hemolytic disease of the newborn and neonatal thrombocytopenic purpura. The hypoferremic state of the mother during pregnancy contributes to the lack of iron reserves in the newborn and predisposes the young child to a state of iron deficiency during the period of rapid growth and throughout the stress situations offered by the recurrent infections of early childhood.

After the first two years of life severe anemias are seldom of nutritional origin, but are more commonly due to primary disorders of the hematopoietic system, the precise nature of which is slowly being revealed by investigations in the rapidly expanding field of pediatric hematology. The detection of hemagglutinins in the hemolytic anemias, platelet agglutinins in the thrombocytopenic purpuras, and the discovery of new types of abnormal hemoglobins have contributed new tools for further research in this field and the understanding of anemias in general.

REFERENCES

1. Bruton, O., Crosby, W. H., and Motuisey, A.: Hereditary Nonspherocytic Hemolytic Anemia Presenting as Hemolytic Disease of the Newborn Infant. Pediatrics, *13*:41, 1954.
2. Burchenal, J., and others: Clinical Evaluation of a New Antimetabolite, 6-Mercaptopurine, in the Treatment of Leukemia and Allied Diseases. Blood, *8*:965, 1953.
3. Cartwright, G. E.: The Anemia of Infection, in Advances in Pediatrics. Chicago, Year Book Publishers, Inc., 1953, Vol. 5, pp. 165, 226.
4. Diamond, L. K.: in Year Book of Pediatrics. 1954–55, p. 308.
5. Estren, S., Suess, J. F., and Dameshek, W.: Congenital Hypoplastic Anemia Associated with Multiple Developmental Defects (Fanconi Syndrome); Report of Case. Blood, 2:85, 1947.
6. Fanconi, G.: Familiare infantile perniziosaartige Anämie. Jahrb. f. Kinderh., *117*: 257, 1927.
7. Farber, S., and others: Symposium on Antifolic Acid Drugs. Blood, 7 (Supp.), Jan., 1952.
8. Gellis, S. S.: Editorial note, in Year Book of Pediatrics. Chicago, Year Book Publishers, Inc., 1953–54, p. 289.
9. Haden, R. L.: Mechanism of Increased Fragility of Erythrocytes in Congenital Hemolytic Jaundice. Am. J. M. Sc., *188*:441, 1934.
10. Harrington, W. J., Minnich, V., Hollingsworth, J. W., and Moore, C. V.: Demonstration of Thrombocytopenic Factor in Blood of Patients with Thrombocytopenic Purpura. J. Lab. & Clin. Med., 38:1, 1951.
11. Herrick, J. J.: Peculiar Elongated and Sickle-Shaped Red Cell Corpuscles in a Case of Severe Anemia. Arch. Int. Med., *6*:517, 1910.
12. Hsia, D. Y.-Y., Allen, F. H., Jr., Gellis, S. S., and Diamond, L. K.: Erythroblastosis Fetalis; Studies of Serum Bilirubin in Relation to Kernicterus. New England J. Med., *247*:668, 1952.
13. Joseph, H. W.: Iron Metabolism and the Hypochromic Anemias. Medicine, 32: 125, 213, 1954.
14. Kaplan, E., Zuelzer, W. W., and Neel, J. V.: New Inherited Abnormality of Hemoglobin and Its Interaction with Sickle Cell Hemoglobin. Blood, 6:1240, 1951.
15. Langley, F. A.: Haemopoiesis and Siderosis in Foetus and Newborn. Arch. Dis. Childhood, 26:64, 1951.
16. May, C. D., Hamilton, A., and Stewart, C. T.: Experimental Megaloblastic Anemia and Scurvy in the Monkey. J. Nutrition, 49:121, 1953.
17. Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C.: Sickle Cell Anemia, Molecular Disease. Science, *110*:543, 1949.
18. Pierce, M.: Proceedings of 2nd National Cancer Conference, 1952, Vol. 1, p. 608.
19. Schulman, I., and Smith, C. H.: Fetal and Adult Hemoglobin in Hemolytic Disease of the Newborn. Am. J. Dis. Child., *87*:167, 1954.
20. Sturgeon, P.: Studies of Iron Requirements in Infants and Children. Pediatrics, *13*:107, 1954.
21. Van Buckem, F. S., Samson, N., and Nieweg, I.: Acta med. Scandinav., *149*:17, 1954.

920 East 59th Street
Chicago 37, Illinois

INTERPRETATION OF HEART MURMURS

JOHN A. BIGLER, M.D.

A heart murmur is not a presenting symptom, but it may become one when the family has been informed that their child has a cardiac murmur. It has been estimated that in 50 to 75 per cent of all children a heart murmur is heard at some time. Because of this frequency, the interpretation of the murmur is important.

If one is familiar with the location and characteristics of cardiac murmurs, one can frequently make the proper interpretation of the underlying lesion without extensive procedures other than a good history and a complete physical examination. Additional information and help may be obtained from roentgenograms, fluoroscopy, the electrocardiogram and such laboratory data as the blood cell count and the sedimentation rate. We shall not consider here those more complex cases of cardiac pathology that require complicated and extensive laboratory facilities.

HEART SOUNDS

In infants and children the heart sounds are louder than in adults because of the thinness of the chest wall. The first sound is louder than the second sound at the apex of the heart, which is in the fourth left interspace just inside the nipple line. The first sound is thought to be due primarily to the closure of the mitral and tricuspid valves and secondarily to the opening of the aortic and pulmonary valves, residual atrial vibration, and acceleration of blood flow from ventricular systole.

The second sound is louder than the first sound in the pulmonic area, which is in the second interspace just to the left of the sternum. The second sound is due to the closure of the aortic and pulmonic valves and may be influenced by the opening of the mitral and tricuspid valves as well as by arterial wall vibration and ventricular relaxation.

If the heart sounds are not heard best in the areas described, one must think of cardiac enlargement, a shift of the heart to the left or right, or other cardiac pathology.

A third sound may be heard. This may be due to a splitting or duplication of the first or second sound. Most commonly in children the third heart sound at the apex is due to a duplication of the second sound and occurs about 0.1 second after the second sound. It is a short sound less loud than the other two sounds. It may be heard in normal children. It is thought to be due to the opening snap of the mitral and tricuspid leaflets and vibration of the ventricular walls. It is important to differentiate this third sound from a mid-diastolic rumble, the latter being indicative of cardiac pathology. At the pulmonic area there may be a splitting of the second sound. This sound may be closely or widely split. It is thought to be due to asynchronous closure of the aortic and pulmonic valves or the opening snap of the mitral valve. A closely split second sound in the pulmonic area may not be abnormal, but splitting of this sound is frequently present in mitral stenosis and bundle branch block.

At times the apical second sound is as loud as or louder than the first sound. In such instances one must consider a prolonged P-R interval. When this interval is prolonged, the mitral leaflets may float back slower than normal and thus close with less of a snap, thereby decreasing the first sound.

MURMURS

To evaluate a murmur properly it must primarily be related to the first or second heart sound. Systolic murmurs usually begin with the first sound and occur for a variable period up to the second sound. Diastolic murmurs may begin with the second sound or may occur in mid-diastole, or they may occur just before the first sound, when they are called presystolic.

There has been a great deal of speculation as to the mechanism of murmurs. Transmission undoubtedly depends upon the tissues through which the sound must travel. The direction of the blood flow may also be a factor. Murmurs are probably produced by the rush of blood from one chamber to another when there has been a relative change in size between the two. Additional factors may be eddies of blood, speed of blood flow and vibration of heart valves, heart walls and great vessels. These explanations are mainly theoretical.

Characteristics of Murmurs

By taking into consideration certain factors one can gain both specific and general information as to the significance of a cardiac murmur.

Here experience is the greatest teacher, experience in the interpretation of what one hears correlated with clinical and pathologic material. In every heart murmur the following should be noted:

Timing. One times the murmur from the first or second heart sound. Systolic murmurs usually begin with the first heart sound and last for a variable period during systole. Diastolic murmurs may begin with the second heart sound as in a ductus arteriosus or an aortic regurgitation at the base of the heart. At the apex of the heart the diastolic murmur usually occurs after the second sound as a mid-diastolic or presystolic murmur. In only far advanced rheumatic carditis in later childhood does the diastolic murmur at the apex extend through most of diastole.

Intensity or Loudness. Grades of I to VI are usually used to denote the intensity of the murmur.

Quality. By quality is meant the character or the individual tone or quality of sound that is heard. Most of the acquired systolic murmurs can be described as blowing, whether soft, loud or high-pitched at the apex. Also in the acquired group is the blowing diastolic murmur in the pulmonic area and the mid-diastolic rumble at the apex. Most congenital heart disease murmurs are rough, coarse or harsh, while those called physiologic or functional (innocent) are hollow to musical.

Location of Greatest Intensity. Although murmurs are heard over small to wide areas, the point of greatest intensity should be recorded. This is often of great importance in determining the site of the lesion.

Transmission. The area as well as the direction of transmission of the murmur depends upon the transmitting tissues between the origin of the murmur and the surface of the chest as well as upon the direction of the blood flow.

Cardiac Rhythm. This may be influenced by the murmur. A mid-diastolic or presystolic murmur at the apex may produce a triple rhythm or three heart tones not normally spaced.

Miscellaneous. While listening to the heart one also notes the color of the patient, the symmetry of the chest and the presence of neck, suprasternal and precordial pulsations.

Evaluation of Cardiac Murmurs

No complete evaluation for every cardiac murmur that occurs can be given in this short discussion. However, physiologic murmurs, acquired murmurs and those of congenital heart disease can usually be differentiated from each other by the history, physical examination and characteristics of the murmur. The physiologic, or innocent, and acquired murmurs are usually characteristic enough to allow for a specific diagnosis. Such is not the case, however, with many murmurs of congenital heart disease. The same type of murmur may be present in a variety of

malformations that require extensive laboratory procedures for diagnosis. In most cases the diagnosis of congenital heart disease can be made from the murmur and the physical examination, and in some the specific lesion identified.

Physiologic or Innocent (Functional) Murmurs

These are present in about 35 to 50 per cent of all children at one time or another. They may come and go. They are usually systolic in time, not widely transmitted, and are best heard in the second to third interspace just to the left of the sternum. They are usually hollow-sounding, but sometimes musical. Most often they range from grade I to II. They may change in intensity, even disappearing upon change in position of the patient. Speeding the heart rate will also decrease the murmur. We examine all patients in the supine position first.

Hemic murmurs have the same characteristics as those just described. They are often transmitted to the neck vessels and, when the hemoglobin is 5 gm. or below, may be heard over the temporal artery in front of the ear or over the lateral skull. On correction of the anemia they disappear.

A loud venous hum in both diastole and systole is heard at times in the second interspace to the left and right of the sternum and transmitted into the neck. It is low-pitched and not harsh like that of a patent ductus murmur and will disappear with the patient in the supine position.

These murmurs are often confused with those of acquired and congenital heart disease.

Acquired Organic Murmurs

In children these murmurs are practically always due to the carditis of rheumatic fever and chorea. They usually have characteristics of timing, quality, location and transmission.

Apical Blowing Systolic Murmur. This murmur has a blowing quality all the way from a soft grade I to a loud blowing grade IV. It is heard best at the apex and is transmitted best to the left toward the axilla. It is the first murmur of rheumatic carditis and is due to mitral regurgitation. This incompetency is probably due to the myocarditis and moderate relaxation of the mitral valve. It is heard well with the patient in the supine position and even better if the patient is rotated toward the left side. There may be accentuation of the second pulmonic sound. The murmur may disappear with recovery. In more severe rheumatic carditis the murmur may become high-pitched and have what is called

a seagull quality. Then transmission increases from the sternum to apex.

Apical Mid-diastolic Murmur. This murmur is a rumble and is not blowing in type. It is definitely longer and later in diastole than a third heart sound. It is heard best just inside the apex, and its transmission is limited. It can usually be accentuated by increasing the pulse rate and turning the patient on his left side. There may be accentuation or splitting of the second pulmonic sound. Early in rheumatic carditis it is often difficult to differentiate the mid-diastolic murmur from a third heart sound. When due to rheumatic carditis, it is usually accompanied by a systolic blow at the apex and may mean an early mitral stenosis. It may disappear with recovery from the carditis, but this is less likely than when only the systolic murmur is present. When mitral stenosis is severe, the diastolic murmur may fill most of the diastole phase of the cycle, but this is present only in older patients after repeated attacks of rheumatic fever.

A mid-diastolic or a diastolic murmur at the apex is sometimes heard in congenital heart disease such as atrial septal defects. In such instances the blowing apical systolic murmur is not present. There is also then the rough to harsh systolic murmur best heard in the second to fourth left interspace of the septal defect. If a mitral stenosis is present with an atrial septal defect (Lutembacher's syndrome), then an apical presystolic murmur will also be heard.

Apical Presystolic Murmur. This murmur is heard late in diastole and is a crescendo blowing sound up to the first heart tone, after which the systolic and mid-diastolic murmurs are usually but not always heard. This gives a triple rhythm. The presystolic is a murmur of mitral stenosis and is often accompanied by a splitting of the second pulmonic sound and presystolic thrill. This murmur is a late manifestation of rheumatic carditis.

Aortic Diastolic Murmur. This is a blowing type of murmur beginning with the loud pulmonic second sound, and in the younger children is heard best in the third interspace just to the left of the sternum. It is transmitted downward and to the left. It may be short or it may fill most of diastole. In older children it may be heard best under the sternum or in the second interspace to the right of the sternum. It is better heard with the patient in the upright position.

Aortic regurgitation produces this murmur. It is rarely heard except after recurrent or prolonged rheumatic infections and is usually accompanied by apical systolic and mid-diastolic murmurs. It is accompanied by a water-hammer pulse, a wide pulse pressure and a capillary pulse. The difference between the systolic and diastolic blood pressure is much wider than normal. In children it is rarely accompanied by the rough systolic murmur of aortic stenosis.

Tricuspid and Pulmonic Murmurs. These murmurs may occur with pancarditis or repeated rheumatic endocarditis. Because their characteristics and timing are so similar to those already mentioned, it is difficult to differentiate them, and they are rarely present when the other acquired murmurs are absent.

Friction Rub. This is not a cardiac murmur. It is a scratchy, scraping or leathery sound due to pericarditis. It is different in sound from a heart murmur and has no direct relationship to the heart tones. It may be part of a rheumatic carditis or may be due to an isolated or nonrheumatic pericarditis. If it is due to rheumatic carditis, there are always one or more of the foregoing murmurs also present. It is usually heard best toward the base of the heart, and is not persistent, but comes and goes.

Murmurs of Congenital Cardiac and Great Vessel Malformations

Such murmurs can usually be described as rough, coarse or harsh in type, systolic in time, with occasionally a diastolic component. They are most often heard best near the base of the heart and have varying degrees of transmission. Though the murmurs of rheumatic carditis are due to myocarditis or endocardial valvular changes, those of congenital origin are due to any one or more of a large number of possible anomalies. For instance, in an intra-atrial septal defect the murmur is systolic in time, yet the contraction of the atria with the passage of blood through the defect is in diastole. It seems unlikely, then, that the murmur is directly due to the passage of blood through the defect. It has been postulated that the murmur is due to the increased amount of blood which must enter the right ventricle being forced into the pulmonary artery. Usually the murmurs of congenital heart malformations are not as characteristic of individual lesions as are those of acquired heart disease. There are exceptions, though, as in typical ductus arteriosus and aortic or subaortic stenosis.

Only the more common typical murmurs or malformations will be considered.

Ductus Arteriosus. Characteristically, in the usual case there is a machinery-like continuous systolic and diastolic murmur—grades III to VI going through the whole cardiac cycle. It is best heard in the first interspace about an inch or two to the left of the sternum, distributed over the base of the heart and accompanied by a thrill, a bounding pulse, a wide pulse pressure, a capillary pulse and little cardiac enlargement. In early infancy only a systolic murmur may be present.

Atrial Septal Defect. This defect may be an isolated lesion or may

be only part of a more complex malformation. When present alone, the murmur is a rough to coarse one of variable intensity, grades I to III, heard best in the second to third interspace just to the left of the sternum and not widely distributed. The second pulmonic sound is often accentuated or split, and at times there is a short diastolic murmur at the apex. A thrill may be palpated.

Ventricular Septal Defect. This, too, may be an isolated lesion or may be part of a more complex malformation. When present alone, the murmur is systolic in time, grade II to IV, and heard best in the third to fourth interspace just to the left of the sternum. It is usually a coarse to harsh murmur with variable transmission and often accompanied by a thrill.

Aortic or Subaortic Stenosis. This is a harsh, short systolic murmur, grade II to IV, heard best in the second interspace to the right of the sternum and transmitted upward into the neck. A thrill is palpated up into the suprasternal notch. This is one of the few murmurs in children heard best to the right of the sternum except when a dextrocardia is present.

Aortic Pulmonary Artery Septal Defect. This is not a common anomaly, but it does have a fairly characteristic murmur. There is a harsh systolic and diastolic murmur shorter than that of a ductus arteriosus, heard best under the sternum or in the second to third left interspace. It is not widely distributed. A rough thrill is present.

Coarctation of the Aorta. ADULT TYPE. There is usually a rough systolic murmur heard best over the second to third left interspace and not widely distributed. Characteristically, there is usually a visible pulsation in the suprasternal notch, a palpable thrill there and absence or marked decrease in the femoral pulse. The blood pressure in the arms is high and absent to low in the legs. The diagnosis can first be suspected by palpation of the femoral artery pulsation in every infant and child.

Tetralogy of Fallot, Pure Pulmonary Stenosis, Tricuspid Atresia, Transposition of the Great Vessels and *Eisenmenger Complex.* Murmurs may not be present in early infancy. When present, they are systolic in time, of an intensity of grade I to III, not widely distributed, and heard best in the second to third interspace to the left of the sternum. A thrill may be present. The murmurs are not characteristic of any specific lesion. Cyanosis is present early in tetralogy of Fallot, tricuspid atresia, transposition of the great vessels and in pulmonary stenosis with intact ventricular septum when severe. It occurs later in the Eisenmenger complex and in tetralogy of Fallot and pure pulmonary stenosis when mild.

Liver pulsation may be palpable in tricuspid atresia and pure pulmonary stenosis.

TABLE 7. *Cyanosis in Congenital Cardiac and Great Vessel Malformations*

I. NO CYANOSIS
- A. Septal defects—usually
- B. Ductus arteriosus
- C. Mild pure pulmonary stenosis
- D. Coarctation of the aorta
- E. Right coronary artery
- F. Fibroelastosis
- G. Glycogen storage disease (cyanosis may be present during decompensation)

II. CYANOSIS EARLY
- A. Severe tetralogy of Fallot
- B. Tricuspid atresia
- C. Transposition of great vessels
- D. Isolated dextrocardia or levulocardia
- E. Large septal defects making a 2- or 3-chambered heart
- F. Severe pulmonary stenosis with intact ventricular spetum

III. CYANOSIS LATE
- A. Eisenmenger complex
- B. Mild pure pulmonary stenosis
- C. Mild tetralogy of Fallot
- D. Large septal defects

707 Fullerton Avenue
Chicago 14, Illinois

JAUNDICE IN INFANCY

SYDNEY S. GELLIS, M.D.

DAVID YI-YUNG HSIA, M.D.

Nearly 40 years ago Holmes[13] summarized the problems of jaundice in infancy in the following words:

> Icterus is a common phenomenon during the first few weeks of life. It occurs as icterus neonatorum in 30 to 80 per cent of all newborn infants. It usually appears about the third day, increases in severity for two or more days, and then slowly disappears. In moderately severe cases, it may be marked for about a week, and in severe cases, for about two weeks. When icterus persists for longer than two weeks and when it increases in intensity towards the end of the second or third week, a more serious condition is suspected.

Although these basic concepts remain unchanged to this day, much has been accomplished towards their clarification. The present paper will outline these developments so that the clinician will be in a better position to diagnose and manage infants with jaundice.

The study of jaundice is greatly facilitated by the use of a micromethod for the determination of serum bilirubin.[18] This technique is adaptable to all standard photoelectric colorimeters and requires only 0.05 to 0.1 ml. of serum from capillary blood,[11] permitting the physician to obtain samples from infants as frequently as indicated with no harmful effects.

JAUNDICE DURING THE FIRST WEEK

The principal causes of jaundice from birth to seven days of age are listed in Table 8. All these conditions are characterized by elevation of total bilirubin, the one-minute or "direct" bilirubin remaining within normal limits throughout.

From the Department of Pediatrics, Harvard Medical School, Boston.

TABLE 8. *Causes for Jaundice during the First Week of Life*

I. PHYSIOLOGIC JAUNDICE
  A. Full term infant
  B. Premature infant
II. ERYTHROBLASTOSIS FETALIS
  A. Rh incompatibility
  B. ABO incompatibility
  C. Other blood group incompatibilities
III. INFECTIONS
  A. Sepsis
  B. Syphilis
  C. Toxoplasmosis
  D. Cytomegalic inclusion cell disease

Physiologic Jaundice in the Full Term Infant

Approximately two thirds of all full term infants have physiologic jaundice during the first week of life[5, 26] (Table 9). This is characterized by a slight but definite elevation of total serum bilirubin in the cord blood at birth. The jaundice reaches a peak between 48 and 72 hours of age and then fades to normal adult levels by the end of the first week. Serum bilirubin seldom exceeds 10 mg. per 100 ml. at its peak in full term infants and usually does not exceed 7 mg. in most instances. As a result, icterus may be mild in many newborn infants, since jaundice makes its appearance in newborn infants only when the bilirubin exceeds 4 mg. per 100 ml., whereas in the average adult it begins to appear when the bilirubin is between 1 and 2 mg.

The exact etiology of physiologic jaundice is still incompletely understood. Weech and his co-workers[9, 26] have felt that it is primarily a reflection of liver immaturity. More recently evidence has been presented to show that it may also result from the excessive breakdown of red blood cells soon after birth.[16, 17] In all likelihood it represents a combination of the two factors, an increased breakdown of fetal red cells which are no longer required after birth, and a functionally immature liver which is unable to excrete this excessive load of pigment.

Physiologic Jaundice in the Premature Infant

Physiologic jaundice in the premature infant tends to be more marked than in the full term infant[19, 24] (Table 9). Although the rise of serum bilirubin at birth and for the first two days of life corresponds closely to that in the full term infant, the bilirubin in the premature infant continues to rise through the third, fourth and sometimes fifth days before exhibiting a downward trend. Because of this, the icterus frequently does not disappear until the end of the second week. Total serum bilirubin levels frequently exceed 20 mg. per 100 ml. at the peak of jaundice. This rise, however, need not be confused with that of

TABLE 9. *Average Total Serum Billirubin Levels in Milligrams per 100 Ml.*

	CORD BLOOD	FIRST DAY	SECOND DAY	THIRD DAY	FOURTH DAY	FIFTH DAY
24 Normal full term infants	2.1 (0.2–5.9)	5.7 (3.0–10.4)	6.8 (0–12.4)	6.1 (0–13.2)	4.7 (0–12.3)	4.2 (0.3–10.6)
15 Normal premature infants	1.3 (0–2.9)	5.4 (0–10.3)	8.1 (0–15.3)	10.7 (0–21.6)	11.2 (0.6–27.0)	11.2 (0.7–21.3)
12 Infants with erythroblastosis due to Rh incompatibility	5.0 (2.5–9.1)	16.5 (8.0–31.8)	15.5 (6.5–25.5)	10.9 (1.4–17.6)	7.9 (2.8–13.5)	——
21 Infants with erythroblastosis due to ABO incompatibility	2.9 (2.4–3.7)	13.4 (6.0–24.0)	16.0 (4.4–27.0)	12.9 (3.0–29.0)	11.9 (2.8–30.0)	——

The normal full term infants are compared with premature infants, infants with erythroblastosis due to Rh incompatibility and ABO incompatibility. The range of bilirubin levels is expressed in parentheses after the average values for the groups.

erythroblastosis fetalis, since the rise in the latter occurs at a much earlier period.

The increased severity of physiologic jaundice in premature infants probably reflects a greater degree of liver immaturity, since there is little evidence to show that the rate of red cell destruction is greater in premature than in full term infants.[5] In this connection it is interesting to note that the bilirubinemia is greater in infants who are premature according to gestational age than in those whose prematurity is based solely on weight.

Until recently physiologic jaundice in both full term and premature infants was regarded as benign and of little significance. However, a number of reports[2, 6, 28] have appeared relating kernicterus to jaundice in several infants in whom a diagnosis of erythroblastosis was excluded. Although, at present, insufficient data are available to evaluate the incidence of this occurrence, exchange transfusion may be indicated for premature and even full term infants who become excessively jaundiced, in order to prevent kernicterus.

Erythroblastosis Due to Rh Incompatibility

The fundamental cause of erythroblastosis fetalis is incompatibility between the fetus and mother with respect to one of the blood group

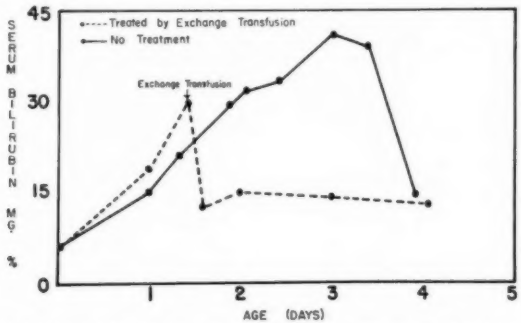


Fig. 5. Total serum bilirubin levels of an infant with erythroblastosis due to RH incompatibility who received no treatment, as compared with one who was treated by exchange transfusion.

factors. When the mother lacks a blood factor present in the red blood cells of the fetus, she may become sensitized to it and produce antibodies which diffuse through the placenta into the fetal circulation and react with the blood factor present in the fetal red blood cells. This alters the cells in some manner, resulting in a much decreased life span for the cells. To compensate for the short survival of its erythrocytes,

the fetus produces new cells much more rapidly than usual. When the baby is born, anemia is not an important problem except in a few cases, but because red blood cells are being destroyed rapidly, and much bilirubin is presented to an immature liver, the elimination of bilirubin immediately becomes a grave problem.[3]

Turning first to erythroblastosis due to Rh incompatibility, the average total serum bilirubin levels in these infants are shown in Table 9.[19, 20] It is evident that the levels in these infants are much higher than in normal infants and that the average age at which the

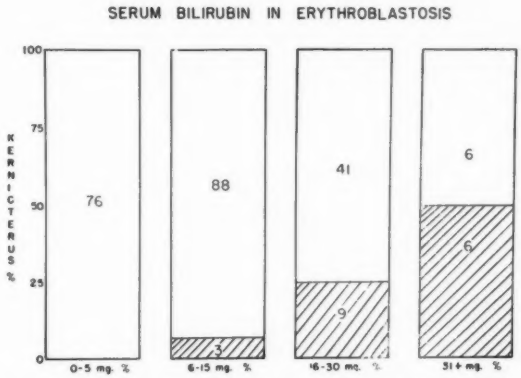


Fig. 6. Serum bilirubin levels and incidence of kernicterus in 229 infants with erythroblastosis. (Figures in shaded areas represent the babies with kernicterus, and figures in clear areas those without kernicterus.) (From Hsia, Allen, Gellis and Diamond: New England J. Med., Vol. 247.)

maximum level is reached is less than two days. The rapidity of rise of serum bilirubin in erythroblastosis eliminates confusion with physiologic jaundice in the premature infant.

Exchange transfusion will markedly lower the total serum bilirubin level, as shown in Figure 5.[20] This drop is due to a combination of removal of approximately 85 per cent of the baby's circulating red cells, which are the only important source of bilirubin, and removal of circulating bilirubin itself. There is usually an upward rise of bilirubin in the hours immediately following the transfusion. This is probably due primarily to the re-equilibration of plasma and extravascular bilirubin.

A most important complication of erythroblastosis fetalis is brain damage, commonly known as kernicterus, which in the past affected about 15 per cent of liveborn infants with erythroblastosis. Almost 70 per cent of babies with kernicterus die within seven days of birth, and many of the remainder succumb during the first year to infection. Kernicterus is thus the most important cause of postnatal death in erythro-

blastosis. Infants with kernicterus who do not die have permanent neurologic sequelae and constitute perhaps 10 per cent of all cases of cerebral palsy. The relationship of jaundice to kernicterus has been suggested[4, 23] and proved by serum bilirubin measurements, as shown in Figure 6.[20] In the cases in which the peak bilirubin fell between 0 and 5 mg. per 100 ml., there was no kernicterus, and in those in the 6 to 15 mg. range there was a 3 per cent incidence of kernicterus. Kernicterus occurred in 18 per cent of the infants whose peak serum bilirubin was recorded at a level between 16 and 30 mg. and in 50 per cent of those in whom levels above 30 mg. were found. As a result, we have kept total serum bilirubin levels below 20 mg. per 100 ml. through the use of one or more exchange transfusions without a single instance of kernicterus in the last 300 successive infants with erythroblastosis treated in this manner.

Erythroblastosis Due to ABO Incompatibility

One of the infrequently recognized causes of jaundice during early infancy is that of erythroblastosis due to ABO incompatibility. Unlike infants with erythroblastosis due to Rh incompatibility, most of the infants with this condition have only moderate jaundice, little or no anemia or hepatosplenomegaly, and recover spontaneously. The disease affects firstborn infants with about the same frequency as later infants in contrast with erythroblastosis due to Rh incompatibility. The diagnosis is difficult to establish because the Coombs test is negative in this condition and the maternal anti-A or anti-B titers are highly variable.

In order to ascertain the incidence of erythroblastosis due to ABO incompatibility a controlled study was undertaken over an 18 month period in one of the nurseries in our hospitals.[15] All the nurses were specifically instructed to look for and to report any infant who was jaundiced in the first 36 hours of life. Of 4175 infants delivered during this period, there were 31 infants reported. Of these, 30 were found to have erythroblastosis due to ABO incompatibility, and one was found to have normal bilirubin levels and no blood group incompatibility between the infant and mother. There were 21 infants with erythroblastosis due to Rh incompatibility during the same period. It is interesting to note that less than ten cases of erythroblastosis due to ABO incompatibility were found at one of the other hospitals with about equal numbers of deliveries during the same period, but where daily reports of jaundice were not requested of the nurses. It appears that erythroblastosis due to ABO incompatibility occurs much more frequently than has been hitherto reported. It may not be diagnosed because the icterus in the infant is attributed to physiologic jaundice or is not considered

to be significant once the possibility of Rh incompatibility has been satisfactorily ruled out.

The total serum bilirubin levels in infants with erythroblastosis due to ABO incompatibility are given in Table 9. The levels are higher than the maximum levels seen in normal infants,[19] and all except one infant showed levels exceeding 10 mg. per 100 ml. Since no one test is diagnostic of this condition, we believe that a diagnosis can be made and treatment initiated on the basis of the following three criteria: (1) jaundice in the first 24 hours, (2) serum bilirubin levels of 10 mg. or higher at 24 hours or less, (3) major blood group incompatibility between infant and mother in the presence of a negative Coombs test. In all our cases the diagnosis of erythroblastosis due to ABO incompatibility was subsequently confirmed by the usual tests, including antibody titers in the mother's and infant's serum, positive two-stage antiglobulin test,[15] spherocytosis on smear, and changes in osmotic and mechanical fragilities.

Since kernicterus does occur in infants with erythroblastosis due to ABO incompatibility,[27] exchange transfusions should be performed if the serum bilirubin exceeds 20 mg. per 100 ml. In our series, eight of the 21 cases required such therapy.

Erythroblastosis Due to Other Blood Group Incompatibilities

Erythroblastosis fetalis can be caused by blood group factors other than Rh and ABO, as shown in Table 10. These factors are uncommon

TABLE 10. *Blood Group Incompatibilities Which May Cause Erythroblastosis Fetalis*

AB	A-B-O "family"
D (= "Rh"), **CC^{w}c**, **Ee**	Rh "family"
Kk	Kell "family"
M, **Ss**	M-N-S "family"
Jk^{a}	Kidd "family"
Fy^{a}	Duffy "family"

(From F. H. Allen, Jr., in Seventh M & R Symposium on Erythroblastosis Fetalis. Columbus, Ohio, M & R Laboratories, 1954.)

or rare causes of erythroblastosis, though all have been incriminated in specific cases at one time or another. All are characterized by a positive Coombs test. Since brain damage is always a threat in erythroblastosis, no matter which blood factor is involved, early diagnosis is of great importance so that exchange transfusions may be given before jaundice becomes too marked.

Infections in the Newborn Period

Jaundice may occur during the newborn period in association with various infections such as sepsis, syphilis and toxoplasmosis. In each of these instances jaundice may be due to excessive hemolysis of red cells, but may also be caused by damage to the hepatic cells, in which case the one-minute or direct bilirubin as well as the indirect will be elevated, thus aiding in distinguishing these conditions from physiologic jaundice or jaundice due to erythroblastosis. A history of early rupture of membranes should make one suspicious of sepsis, and lesions of the skin and mucous membranes should alert one to the possibility of syphilis. In the absence of a suggestive history or diagnostic physical findings, the infant with early and severe jaundice who has no blood incompatibility with his mother's blood should receive definitive study with a view to the diagnosis of any one of these infections.

Cytomegalic Inclusion Cell Disease. Recently, France[10] reported a series of 23 cases of cytomegalic inclusion cell disease in infants. Intranuclear inclusion bodies were found in one or more organs in each of these cases. The most common clinical picture was that of infants dying within a few days after birth with jaundice, purpura, hepatosplenomegaly and erythroblastemia with diminution of blood platelets. Cerebral calcifications have also been reported. Except for the absence of blood group incompatibility, these infants cannot be differentiated from those with erythroblastosis fetalis. Examination of concentrated urine sediment for inclusion bodies should be performed if no explanation for jaundice has been found.

JAUNDICE AFTER THE FIRST WEEK

The principal causes of jaundice in infancy after the first week of life are listed in Table 11. Except for the hemolytic anemias, all are characterized by elevations of both one-minute and total serum bilirubin. Since elevation of one-minute direct bilirubin rarely occurs in the vari-

TABLE 11. *Causes of Jaundice in the Infant after the First Week of Life*

I.	PROLONGED OBSTRUCTIVE JAUNDICE IN INFANCY
	A. Atresia of the bile ducts
	B. Inspissated bile due to erythroblastosis fetalis
	C. Neonatal hepatitis
II.	PROLONGED "PHYSIOLOGIC" JAUNDICE
III.	GALACTOSEMIA
IV.	CONGENITAL FAMILIAL NONHEMOLYTIC JAUNDICE WITH KERNICTERUS
V.	HEMOLYTIC ANEMIAS OTHER THAN ERYTHROBLASTOSIS FETALIS
	A. Congenital hemolytic anemia
	B. Acquired hemolytic anemia
	C. Cooley's anemia
	D. Sickle cell anemia
	E. Hereditary nonspherocytic hemolytic disease

ous causes of jaundice arising in the first week of life, its presence is extremely helpful in distinguishing the following diseases from those already described.

Prolonged obstructive jaundice in infancy[22] makes up the largest group of cases at this age. These are characterized by the following findings: (1) jaundice occurring usually after the first week of life (Fig. 7), (2) moderate hepatomegaly and splenomegaly, (3) increased bilirubin in the urine, (4) absence of bile in the stool, (5) decreased or absent urobilinogen in the urine and stools, (6) negative flocculation

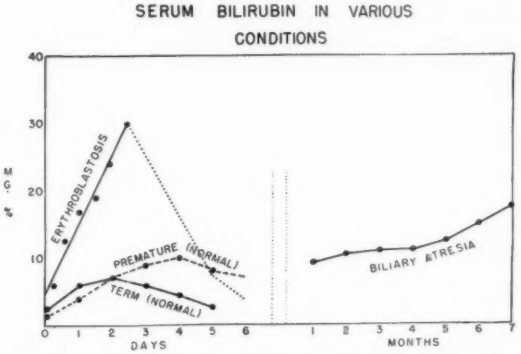


Fig. 7. Serum bilirubin changes in jaundice during the first week of life contrasted with those after the first week.

tests for liver function, and (7) elevation of both one-minute and total serum bilirubin. Each of the causes of prolonged obstructive jaundice will be taken up individually and then differentiated from one another.

Atresia of the Bile Ducts

Approximately 60 per cent of the cases of prolonged obstructive jaundice in infancy are due to atresia of the extrahepatic bile ducts.[22] Infants with this condition usually acquire gradual jaundice starting after the first or second week of life. This is accompanied by dark urine, clay-colored stools, hepatomegaly and splenomegaly. The infants remain well nourished and for the first three or four months may show little evidence of serious disease. Emaciation, rickets due to poor absorption and utilization of vitamin D, and cirrhosis of the liver with varices do not develop until several months have elapsed. In patients whose defects cannot be corrected surgically death usually occurs within the first year. In our series of 106 cases only 20 per cent had anatomic defects amenable to surgical anastomosis, and two thirds of these patients died either during the immediate postoperative period or subse-

quently from biliary cirrhosis. Only six children in this group are living and well and can be considered cured at the present time.

Recently Ahrens and his co-workers[1] reported a number of cases in which atresia of the extrahepatic ducts was accompanied by atresia of the intrahepatic ducts as well. Unlike the atresia of the extrahepatic ducts alone, the course of the disease was distinguished by a relatively long life span, all patients surviving more than three years, with one still alive at five years. Generalized skin xanthomas occurred in all patients together with a marked elevation of the serum lipids. At autopsy there was no indication of intrahepatic bile ducts.

Inspissated Bile Due to Erythroblastosis Fetalis

Fifteen per cent of the cases of prolonged obstructive jaundice in infancy are due to inspissated bile as a result of erythroblastosis fetalis.[22]

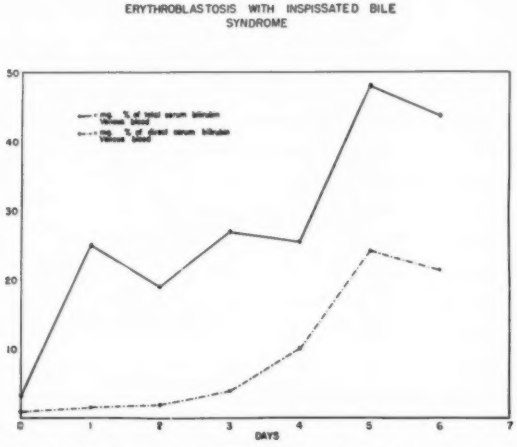


Fig. 8. Inspissated bile due to erythroblastosis fetalis. The one-minute serum bilirubin shows a delayed rise as compared with the total serum bilirubin. (From Hsia, Allen, Gellis and Diamond: New England J. Med., Vol. 247.)

As has been previously shown, the jaundice in most of the infants with erythroblastosis fetalis begins to fade by the fourth or fifth day and is usually gone by the end of ten days. In a few infants, however, the icterus tends to persist and is associated with elevation of one-minute as well as total serum bilirubin (Fig. 8), representing the syndrome of inspissated bile due to erythroblastosis fetalis.

A diagnosis of inspissated bile due to erythroblastosis may be made on the basis of the following criteria: (1) jaundice which appears in

the first 24 hours of life, (2) jaundice which persists for more than the first three weeks of life, (3) an obstructive type of jaundice with elevations of both one-minute and total serum bilirubin, (4) negative flocculation tests, and (5) blood grouping studies showing incompatibility between the infant and mother and definite evidence of erythroblastosis in the infant. Except for the last factor, these cases may easily be mistaken for atresia of the bile ducts. Ten of the 30 patients in the present series were admitted to the hospital for surgical exploration, and the diagnosis of erythroblastosis was not considered prior to admission. It is interesting to note that of the 30 patients studied, only three were known to have what was considered adequate therapy, namely, multiple exchange transfusions with the first one given shortly after birth. All the patients with this condition recovered uneventfully and are alive and well, free from jaundice, passing normally colored stools and have apparently normal liver function. Because of the excellent prognosis, no specific treatment is indicated in this disease.

Neonatal Hepatitis

Finally, 25 per cent of the cases of prolonged obstructive jaundice in infancy are due to neonatal hepatitis.[12] In 1952, when the problem of prolonged obstructive jaundice in infancy was reviewed, we[22] were impressed by a group of infants for whom no specific cause for jaundice could be found. They appeared indistinguishable from the infants with atresia of the bile ducts except that their bile ducts were subsequently found to be patent. It was felt that these cases were the result of various etiologies such as small bile ducts, hepatic immaturity, dehydration, hepatitis, and so forth, and so all infants in this group were tentatively classified as having inspissated bile of unknown etiology. Since then, Craig and Landing[7] have shown on the basis of microscopic studies that these infants had a viral hepatitis, and Stokes and his co-workers[25] have reported that the serum hepatitis virus was apparently transmitted to human volunteers by injection of blood from one of such infants who died and also from his mother.

Neonatal hepatitis[12] is characterized by early onset of jaundice during the first few weeks of life, acholic stools, dark urine and moderate hepatomegaly and splenomegaly. These cases can be differentiated from atresia of the bile ducts only by exploration and liver biopsy or by a study of urine and stool bilirubin and urobilinogen and serum bilirubin levels. Follow-up studies in a group of 42 infants with neonatal hepatitis revealed that 29 (71 per cent) are living and well, four (10 per cent) are living with jaundice and cirrhosis, eight (19 per cent) have died, and one has had incomplete follow-up.

On microscopic examination the liver sections show gross distortion of the liver cell cord pattern with great variations in liver cell size and the presence of multinucleate giant cells diffusely distributed throughout the lobules (Fig. 9).

The pathogenesis of neonatal hepatitis is still incompletely understood. On the basis of the present available evidence, it appears that the virus of homologous serum hepatitis is the most likely cause of neonatal hepatitis and is transmitted across the placental barrier by mothers who are silent carriers of the virus.[12]

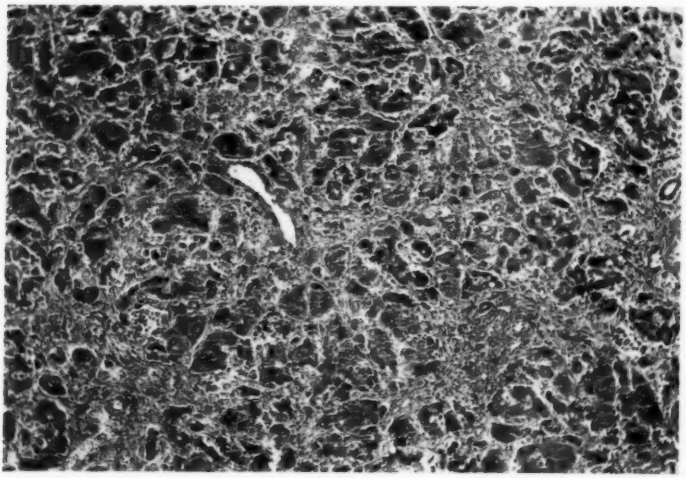


Fig. 9. Photomicrograph of neonatal hepatitis. (From Craig and Landing: Arch. Path., Vol. 59.)

No definitive treatment is available for neonatal hepatitis at present. Supportive measures, such as protein infusions, whole blood, vitamins and an adequate protein intake, are helpful. Extensive surgical study should be avoided, since the infants do poorly, perhaps because of the anesthesia and trauma of surgical exploration. If the diagnosis is in doubt after careful study, it is recommended that a small incision be made, a cholangiogram obtained after injection of dye into the gallbladder, and, if normal extrahepatic ducts are demonstrated, a liver biopsy be obtained and the incision immediately closed. Cortisone given by mouth is useful as a diagnostic and possibly therapeutic tool. In atresia of the bile ducts the hormone has no effect on the obstructive jaundice, while in neonatal hepatitis it will sometimes dramatically lower the bilirubin and relieve the obstruction, although its effect on the ultimate course of the disease remains to be determined.

Differential Diagnosis of Prolonged Obstructive Jaundice in Infancy

The three main causes for prolonged obstructive jaundice in infancy can be differentiated by the combined use of good clinical judgment and a few laboratory tests. In most instances inspissated bile due to erythroblastosis can be diagnosed on the basis of blood grouping tests. Atresia of the bile ducts and neonatal hepatitis are somewhat more difficult to differentiate and may require a period of watchful waiting. In our own clinics, if there is any doubt about the diagnosis, surgical exploration is postponed until repeated examination of the stools and urines together with serial liver function tests, including serum bilirubin, have been performed.

A waiting period for the purpose of obtaining serial studies can be safely undertaken if the infant is seen early in his course. This is especially important in view of the fact that infants with neonatal hepatitis do poorly after operation.

At the end of the period of study, which is one month, surgical exploration is indicated if (1) there has been consistently no bile in the stools and duodenal secretions, (2) there has been no urobilinogen in the urine, (3) the initial bilirubin level was low and has shown a slowly progressive increase with no variability in pattern, (4) the flocculation tests are negative, (5) there is no blood group incompatibility to suggest erythroblastosis.

Operation should be deferred longer if (1) there is bile in the stools or duodenal secretions even in small amounts, (2) urobilinogen is present in the urine in normal dilutions, (3) the initial bilirubin level was high and has shown a tendency to fall or be highly variable with no definite upward trend, (4) the flocculation tests are positive, (5) blood group incompatibility suggesting erythroblastosis can be demonstrated.

It has been found that the differentiation between biliary atresia and inspissated bile due to erythroblastosis and neonatal hepatitis is usually not difficult at the end of the waiting period.

Prolonged Physiologic Jaundice

Newborn infants who have been severely ill during the first week or ten days of life will frequently show a prolongation of physiologic jaundice. In most instances there appears to be inspissation of the biliary secretions with elevations of both the one-minute and total bilirubin levels in the serum. Prolongation of the jaundice has been observed in such conditions as pneumonia, congenital heart disease, renal lesions, after major surgery, and in infants of diabetic mothers with respiratory distress. No treatment is indicated, since the jaundice usually subsides when the infant recovers from the illness.

Galactosemia

The ingestion of lactose in infants with galactosemia causes profound disturbances in the liver which in practically all instances produce obstructive jaundice with elevation of both the one-minute and total serum bilirubin.[21] The jaundice does not appear until after the first week of life and subsides promptly when lactose is removed from the diet, or gradually subsides over a period of days to weeks if lactose is not withheld. In all instances of obstructive jaundice in this age group a careful examination of several urine specimens for reducing substance should be carried out, for early diagnosis and the feeding of a milk substitute will result in the complete disappearance of all abnormal findings caused by this condition. One should be suspicious of galactosemia if a family history is obtained of early obstructive jaundice or cirrhosis in other siblings, since the disease tends to be familial.

Congenital Familial Nonhemolytic Jaundice with Kernicterus

In 1952 Crigler and Najjar[8] reported a new entity in the newborn known as congenital familial nonhemolytic jaundice with kernicterus. The affected infants were from one large family in western Maryland where a great deal of intermarriage had occurred. Jaundice was first noted in the affected infants on the second day of life, and the serum bilirubin levels subsequently rose to 25 to 45 mg. per 100 ml. The elevations were primarily in the indirect fraction, but slight elevations in the one-minute bilirubin were also noted. Most of the affected infants had kernicterus, which was indistinguishable from that seen in erythroblastosis. No abnormal blood groups or antibodies could be demonstrated, and there was no hematologic evidence of hemolytic disease. There was no significant histopathology in the liver. Liver function tests were normal except for a delayed excretion of bilirubin. This condition appears to be a genetic defect in which the infant is unable to excrete bilirubin at a normal rate and may represent a deficiency in an enzyme system.

Hemolytic Anemias

Jaundice may occur as a result of various hemolytic anemias during the first six months of age. This has been observed in congenital and acquired hemolytic anemias, Cooley's anemia, sickle cell anemia and hereditary nonspherocytic hemolytic disease, although crises in these anemias are extremely rare in the early weeks of life and seldom require consideration. All are characterized by elevations of the total bilirubin without a corresponding rise of the one-minute bilirubin. Except in periods of hemolytic crises, the rise seldom exceeds 3 mg. per 100 ml.

SUMMARY

The problems of jaundice in infancy have been greatly clarified through observations made with a micromethod for serum bilirubin requiring only capillary blood. Jaundice during the first week of life is usually caused by (1) physiologic jaundice, (2) erythroblastosis due to Rh, ABO or other blood group incompatibilities, (3) infections, including sepsis, syphilis, toxoplasmosis and cytomegalic inclusion cell disease. After the first week it is usually caused by (1) atresia of the bile ducts, (2) inspissated bile due to erythroblastosis, (3) neonatal hepatitis, (4) prolonged physiologic jaundice, (5) galactosemia, (6) congenital nonhemolytic jaundice with kernicterus, and (7) hemolytic anemias. These conditions are usually easy to differentiate from one another through the use of proper laboratory tests, and especially with the aid of serum bilirubin determinations.

REFERENCES

1. Ahrens, E. H., Jr., Harris, R. C., and MacMahon, H. E.: Atresia of the Intrahepatic Bile Ducts. Pediatrics, *8*:628, 1951.
2. Aidin, R., Corner, B., and Tovey, G.: Kernicterus and Prematurity. Lancet, *1*:1153, 1950.
3. Allen, F. H., Jr., and Diamond, L. K.: Prevention of Kernicterus. J.A.M.A., *155*:1209, 1954.
4. Allen, F. H., Jr., Diamond, L. K., and Vaughan, V. C., III: Erythroblastosis Fetalis. VI. Prevention of Kernicterus. Am. J. Dis. Child., *80*:779, 1950.
5. Blackfan, K. D., and Diamond, L. K.: Atlas of the Blood in Children. New York, Commonwealth Fund, 1944, p. 25.
6. Black-Schaffer, B., Kambe, S., Furuta, M., and Moloney, W. C.: Neonatal Jaundice and Kernicterus. Am. J. Dis. Child., *87*:737, 1954.
7. Craig, J. M., and Landing, B. H.: Form of Hepatitis in Neonatal Period Simulating Biliary Atresia. Arch. Path., *59*:321, 1952.
8. Crigler, J. F., Jr., and Najjar, V. A.: Congenital Familial Nonhemolytic Jaundice with Kernicterus. Pediatrics, *10*:169, 1952.
9. Davidson, L. T., Merritt, K. K., and Weech, A. A.: Hyperbilirubinemia in the Newborn. Am. J. Dis. Child., *61*:958, 1941.
10. France, N. E.: Inclusion Disease in Childhood. Arch. Dis. Child., *26*:588, 1951.
11. Gellis, S. S., and Hsia, D. Y.-Y.: Liver Function Tests in Infants and Children. P. Clin. North America, *2*:177, 1955.
12. Gellis, S. S., Craig, J. M., and Hsia, D. Y.-Y.: Prolonged Obstructive Jaundice in Infancy. IV. Neonatal Hepatitis. Am. J. Dis. Child., *88*:285, 1954.
13. Holmes, J. B.: Congenital Obliteration of Bile Ducts: Diagnosis and Suggestions for Treatment. Am. J. Dis. Child., *11*:405, 1916.
14. Hsia, D. Y.-Y., and Gellis, S. S.: Prolonged Obstructive Jaundice in Infancy. III. Liver Function Tests. Am. J. Dis. Child., *85*:13, 1953.
15. Hsia, D. Y.-Y., and Gellis, S. S.: Studies on Erythroblastosis Due to ABO Incompatibility. Pediatrics, *13*:503, 1954.
16. Hsia, D. Y.-Y., and Page, M.: Coproporphyrin Studies in Children. II. Erythrocyte Coproporphyrin and Protoporphyrin in Normal Infants and Children. Proc. Soc. Exper. Biol. & Med., *86*:89, 1954.
17. Hsia, D. Y.-Y., Goldbloom, R. B., and Gellis, S. S.: Studies of the Mechanical Fragility of Erythrocytes. II. Relation to Physiologic Jaundice of the Newborn Infant. Pediatrics, *13*:24, 1954.

18. Hsia, D. Y.-Y., Hsia, H. H., and Gellis, S. S.: A Micro Method for Serum Bilirubin. J. Lab. & Clin. Med., *40*:610, 1952.
19. Hsia, D. Y.-Y., Allen, F. H., Jr., Diamond, L. K., and Gellis, S. S.: Serum Bilirubin Levels in the Newborn Infant. J. Pediat., *42*:277, 1953.
20. Hsia, D. Y.-Y., Allen, F. H., Jr., Gellis, S. S., and Diamond, L. K.: Erythroblastosis Fetalis. VIII. Studies of Serum Bilirubin in Relation to Kernicterus. New England J. Med., *247*:668, 1952.
21. Hsia, D. Y.-Y., Hsia, H. H., Green, S., Kay, M., and Gellis, S. S.: Amino-Aciduria in Galactosemia. Am. J. Dis. Child., *88*:458, 1954.
22. Hsia, D. Y.-Y., Patterson, P., Allen, F. H., Jr., Diamond, L. K., and Gellis, S. S.: Prolonged Obstructive Jaundice in Infancy. I. A General Survey of 156 Cases. Pediatrics, *10*:243, 1952.
23. Mollison, P. L., and Walker, W.: Controlled Trials of the Treatment of Hemolytic Disease of the Newborn. Lancet, *1*:429, 1952.
24. Obrinsky, W., Allen, E. L., and Anderson, E. E.: Physiologic Hyperbilirubinemia in Premature Infants. Am. J. Dis. Child., *87*:305, 1954.
25. Stokes, J., Jr., and others: The Carrier State in Viral Hepatitis. J.A.M.A., *154*: 1059, 1954.
26. Weech, A. A.: Genesis of Physiological Hyperbilirubinemia. Advances in Pediatrics, *2*:346, 1947.
27. Wiener, A. S., and Brody, M.: Encephalopathy (Kernicterus) of Erythroblastosis Fetalis. Am. J. Ment. Deficiency, *51*:1, 1946.
28. Zuelzer, W. W., and Mudgett, R. T.: Kernicterus: Etiologic Study Based on an Analysis of 55 Cases. Pediatrics, *6*:452, 1950.

330 Brookline Avenue
Boston 15, Mass.

CHRONIC VAGUE ABDOMINAL PAIN IN CHILDREN

JUDITH L. WOOD, M.D.

L. MARTIN HARDY, M.D.

HARVEY WHITE, M.D.

Abdominal pain in children is one of the most common, intriguing and most difficult presenting symptoms to evaluate accurately in the field of pediatrics. This complaint may be initiated by a simple colicky cramp or by conditions that produce the most serious medical emergencies. The manifestations of abdominal pain are protean and the causes legion. Therefore in this clinic we shall review the application of a good history and physical examination, attempt to classify the etiologic factors, demonstrate the use and interpretation of roentgenographic procedures by case studies, and present an analysis of 95 children studied at the Children's Memorial Hospital over a three year period.

HISTORY

This paper is to be limited to vague indefinite abdominal pain. However, in a symposium on presenting symptoms, a review of elementary practical points in history taking and physical examination in children referable to any abdominal pain is pertinent. An accurate story of the complaint from parent and patient is extremely important and difficult to obtain, but repeated interrogation is usually rewarding. In general systemic disease such as upper respiratory infection the abdominal discomfort is usually vague and poorly localized by the patient, the child frequently pointing to the umbilicus when asked where it hurts. If

From the Children's Memorial Hospital, Chicago.

This study was supported by a grant from the Otho S. A. Sprague Institute.

vomiting is associated, especially in younger children, it is helpful to note whether the pain is relieved by vomiting or a bowel movement. In localized infection of the intestinal tract, vomiting rarely relieves pain, and what the child calls pain may be only nausea and cramps preceding active regurgitation or evacuation. Likewise the discomfort and cramps of diarrheas are usually temporarily relieved by defecation. It is of interest to note what position the child assumes and what manipulation may be performed for relief. Pressure and warmth may alleviate the cramps associated with general systemic infections and diarrheas, but not local intestinal infections.

The story of abdominal pain in upper respiratory infections and mesenteric adenitis may be identified with that of an acute appendicitis or infected perforating Meckel's diverticulum. They can defy all attempts at differentiation. The acute appendix or Meckel's diverticulum needs operation, but one should not feel too embarrassed when a typical story and finding of an acute abdominal condition compel him to honestly advise operation, only to find enlarged mesenteric nodes.

Referred pain from chest infections such as pneumonia and pleurisy commonly have the preceding complaint of a cold. The pain is usually localized to the upper abdomen, is more superficial and accentuated by deep breathing.

Pain due to an obstructed viscus is intermittent, slight or intense, depending upon the suddenness of the obstruction. Tenderness is minimal and rigidity rare unless perforation is imminent.

Pain and discomfort originating from a lesion of the genitourinary tract can be one of the most misleading and deceiving symptom complexes to unravel. This is especially true in the small infant when the only history is that of a baby who is somewhat irritable and vomits frequently. Unfortunately in many instances all efforts are directed at repeated formula changes, roentgenograms of the gastrointestinal tract or subdural taps with no relief. Children with some obstruction along the urinary tract by aberrant vessels, valves or bladder neck obstruction frequently present this type of story, and the earlier the true condition is recognized and relieved, the more kidney tissue can be salvaged.

Any history relative to vague abdominal pain is not complete until one has inquired in detail about the health, and of similar complaints within the immediate family or of an admired friend or relative of the child. Fortunately neurosis in children is not too common; however, the doctor often regards vague abdominal pain as such, only to be embarrassed at a later date to find that the child had a malrotation or some congenital malformation that was producing an obstruction of the bowel or genitourinary tract. Even more confusing and difficult to demonstrate in the so-called neurotic child is abdominal pain secondary to allergic conditions or gastrointestinal epilepsy. Also an evaluation of

the patient's threshold to pain should be attempted while taking the history and further judged while examining the subject.

EXAMINATION OF CHILD

The examination of the abdomen of a child is often difficult, and conclusions drawn from one attempt are hazardous if full cooperation is not attained. In the first place wash and warm your hands; then make haste by proceeding cautiously. Small infants are at times more easily examined on the mother's lap or across her shoulders, the doctor making his approach from the rear. A bottle of water or formula for the infant to nurse on is a great adjunct in relaxing abdominal muscles. Most small children object strenuously to having a stranger come in and forcefully place them on their backs and start pommeling their stomachs. Many will tolerate abdominal palpation in the sitting position until the examiner can finally win the patient's cooperation and a more practical position.

Gentleness is a must with continuous contact of the examining hand with the abdomen. Quick movements to different areas cause voluntary resistance from the unpleasantness of the sensation even in normal children. Watch the child's expression; in older children attempt to distract their attention from the examination and allay their fears by a running chatter of their age interests. If areas of tenderness are encountered, attempt to determine whether they are superficial or deep. Superficial tenderness is accentuated when the skin is rolled between the examining fingers, but on gentle deep pressure over the same area no great resistance is felt. Some children are stoics or are afraid to admit pain for fear of the possible consequences that may entrap them into imminent operation. Other children are overwilling to cooperate, expressing their supposed discomfort with a loud "ouch" with any manipulation. In such instances distraction by conversation about their personal interest may change the repeated "ouch" even during deep palpation to a recitation about their pets' latest tricks.

A complete physical examination of the child is essential in evaluating any presenting symptom, and this is true with abdominal pain. For example, pigmentation of the lips may lead to an early diagnosis of intestinal polyps, or a meatus ulcer may explain the pain of a distended bladder. Further discussion of specific conditions is not within the realm of this report, but Table 12 gives most of the causes of abdominal discomfort in children.

MATERIAL

Ninety-five children were investigated because of vague recurrent abdominal pain of two or more months' duration. These children were

TABLE 12. *Etiologic Classification of Abdominal Pain in Children*

I. INFECTIONS
- A. Abdominal abscess
- B. Appendicitis
- C. Central nervous system infection—poliomyelitis, encephalitis, meningitis
- D. Gastrointestinal infections
  1. Specific bacterial
  2. Nonspecific bacterial
  3. Parasitic
- E. Genitourinary infections—pyuria, nephritis, nephrosis, vulvovaginitis
- F. Herpes zoster—thoracic or lumbar
- G. Infectious mononucleosis
- H. Liver disease—hepatitis, cholecystitis
- I. Lung infections with pleurisy
- J. Meckel's diverticulum—infected, perforating
- K. Mesenteric adenitis
- L. Mumps—pancreatitis, oophoritis
- M. Oophoritis, nonspecific
- N. Osteomyelitis
- O. Peritonitis
- P. Regional ileitis
- Q. Rheumatic fever
- R. Septicemia—endocarditis with emboli
- S. Upper respiratory infections

II. OBSTRUCTIONS
- A. Hepatic and intestinal
  1. Congenital
     a. Atresias
     b. Congenital megalocolon
     c. Duplications
     d. Hernias—inguinal, umbilical, diaphragmatic, internal
     e. Malrotation and volvulus
     f. Mechanical obstruction
     g. Meconium ileus
     h. Stenosis
     i. Tumors
  2. Acquired
     a. Biliary tract obstructions
     b. Colic
     c. Constipation
     d. Intussusception
     e. Mechanical obstructions
     f. Polyps
     g. Portal circulation obstruction—cirrhosis of liver, cardiac decompensation
     h. Rectal prolapse
- B. Genitourinary
  1. Congenital
     a. Aberrant vessels
     b. Atresias
        (a) Along urinary tract—ureteral, urethral
        (b) Along genital tract—vaginal, cervical, imperforate hymen
     c. Duplication of kidney
     d. High ureteral pelvic insertion
     e. Polycystic kidney
     f. Stenosis—along genitourinary tract as in atresias
     g. Tumors
     h. Ureterocele

TABLE 12. *Continued*

2. Acquired
   a. Dysmenorrhea
   b. Foreign body
   c. Meatus ulcer
   d. Ovarian cysts
   e. Polyps
   f. Torsion of gonads
   g. Trauma

III. GENERAL SYSTEMIC DISEASES OTHER THAN INFECTIONS
   A. Abdominal epilepsy
   B. Allergies
   C. Blood dyscrasias—purpuras, sickle cell anemia, lymphomas, hemophilia
   D. Metabolic diseases—diabetes
   E. Neurosis

IV. INJURY FROM EXTRINSIC AGENTS AND MISCELLANEOUS
   A. Burns—associated with intestinal ulcers
   B. Foreign bodies
   C. Ovulation
   D. Poisons
   E. Ulcers
   F. Trauma

between the ages of three and 14 years and had complained of abdominal pain on two or more occasions. Examinations were carried out in the Children's Memorial Hospital and in the Hospital Outpatient Department. In all, physical findings were negative or equivocal. There were 43 white females, 25 white males, 14 colored females and 13 colored males.

METHOD

Laboratory and roentgen studies were done in each to determine (1) the incidence of organic pathology, (2) the nature of the lesion, and (3) the laboratory and roentgen studies most likely to demonstrate pathology. The procedures done were (1) complete blood cell count, (2) sickling test of the red blood cells in the colored patients, (3) urinalysis, (4) Harrison spot test of the urine for bile, (5) stool smear and culture for ova, parasites and bacterial pathogens, (6) stool examination for blood by the hematest or benzidine test, (7) stool smear for eosinophils, (8) anal smear for *Enterobius vermicularis* ova, (9) serology (Kahn), (10) Mantoux, 1:1000, (11) upper gastrointestinal roentgenogram, (12) lower gastrointestinal roentgenogram, (13) cholecystogram, and (14) intravenous pyelograms. Psychometric examination and electroencephalogram were done in some cases. Further examinations, such as retrograde pyelography, gastric analysis and exploratory laparotomy, were done in those cases in which they seemed indicated. Appropriate

therapy was instituted in those in whom a specific diagnosis was made; the remainder of the patients were treated symptomatically.

RESULTS

As shown in Table 13, some abnormality was demonstrated in 42 per cent of the cases studied. In 20 per cent, the lesion shown was responsible for the abdominal pain. Relief of symptoms with appropriate treatment and correction of the abnormal laboratory findings were interpreted as evidence that the complaints could be correlated with the findings.

TABLE 13. *Incidence of Pathology*

Number of cases studied	95
Pathology demonstrated in	42%
Pathology related to pain demonstrated in	20%
Unrelated, incomplete and incidental findings in	22%

TABLE 14. *Pathology Demonstrated by Each Procedure*

PROCEDURE	TOTAL PERCENTAGE	SIGNIFICANT PERCENTAGE
1. **Blood cell count:**	5	5
Hemoglobin	1	1
Red blood cell count	1	1
White blood cell count	4	4
Sickling test	0	0
2. **Urinalysis:**	5	5
Routine	4	4
Harrison spot test	1	1
3. **Mantoux**	11	0
4. **Serology**	0	0
5. **Stool examination:**	6	4
Smear for ova, parasites	1	1
Culture	0	0
Smear for eosinophils	2	0
Chemical test for blood	4	3
6. **Gastrointestinal roentgenograms:**	10	7
Upper	9	7
Lower	1	0
7. **Cholecystogram**	1	0
8. **Intravenous pyelogram**	14	4

The percentage of cases showing pathology by each procedure is listed in Table 14. Five per cent showed some abnormality of the blood cell count, and in all these the disturbance was found to be significant. Of the 5 per cent in whom the urinalysis revealed an abnormality, all were significant. Sickling of the red blood cells was not present in any of the 27 colored patients. Although 11 per cent of the patients had positive Mantoux reactions, none had evidence of pulmonary tuberculosis in

TABLE 15. *Relationship of* Enterobius Vermicularis *Infection to Abdominal Pain*

	NUMBER OF CASES	PERCENTAGE POSITIVE
Group with abdominal pain	95	13
Control group	86	15

TABLE 16. *Pathology Related to Abdominal Pain*

	NUMBER OF CASES
1. **Gastrointestinal:**	
Peptic ulcer	6
Small bowel multiple polyposis	1
Appendiceal abscess	1
Hepatitis	1
Ascariasis	1
2. **Genitourinary:**	
Vulvovaginitis	1
Hemorrhagic cystitis	1
Pyelitis	1
Ureteral stricture	2
Ureteral obstruction (aberrant vessel)	1
Ovarian teratoma	1
3. **Miscellaneous:**	
Mesencyclic fits	1

follow-up roentgen examinations of the chest. The serology was negative in all. The stool examination showed an abnormality in 6 per cent, but the disturbance could be related with the symptoms in only 4 per cent. Of the roentgenographic procedures done, only the upper gastrointestinal series and the intravenous pyelogram showed significant pathology. The incidence was 7 per cent in the former and 4 per cent in the latter. Twelve per cent of the cases showed some urinary tract anomaly.

The incidence of *Enterobius vermicularis* infection was thought to be extremely high (13 per cent). For comparison, a control series was carried out on 85 patients who had never had abdominal pain. The incidence of infection was slightly higher in the control group (Table

15). *Enterobius vermicularis* infection was therefore excluded as a possible cause of abdominal pain in this investigation.

There were 18 patients in whom the abnormality demonstrated was shown to be responsible for the complaint of abdominal pain (Table 16). In six patients duodenal ulcer was demonstrated on roentgenographic study. All improved on dietary management, and follow-up roentgenograms have shown disappearance of the ulcer crater. Of these, there were three white boys, ages six, 13 and 14; one eight year old white girl; and two colored boys, ages seven and 11 years. An 11 year old white girl (Case I) had an iron deficiency anemia, blood in the stool, and a

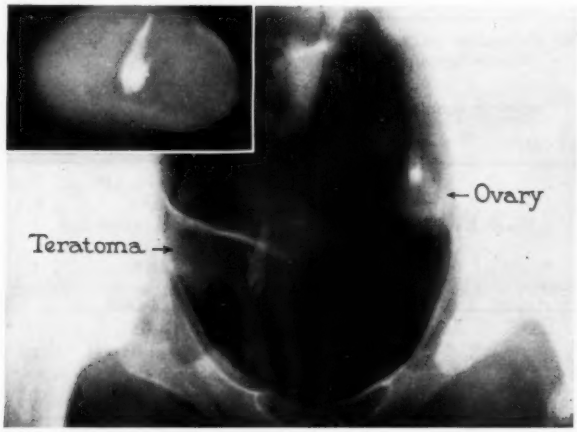


Fig. 10. Pneumoperitoneum outlining large soft tissue mass (teratoma) on the left with a tooth in the center. Normal almond-size ovary is on the right. Roentgenogram of removed specimen is in left upper corner.

small bowel intussusception demonstrated on the upper gastrointestinal roentgen examination. At operation small bowel multiple polyposis was found. A 14 year old white boy with recurrent abdominal pain of four month's duration had a history of appendectomy 17 months previously. On physical examination there was questionable thickening of the cul-de-sac. There was blood in the urine and a white blood cell count of 19,000. Further extensive laboratory studies revealed no additional information. On exploratory laparotomy the distal tip of the appendix was found surrounded by a large abscess. In one five year old white boy the Harrison spot test of the urine was positive for bile. He was subsequently shown to have viral hepatitis. One eight year old colored boy was found to have *Ascaris lumbricoides* ova in the stool smear. In an 11 months follow-up after successful treatment there was no recurrence of pain.

One seven year old white girl with pyuria was found to have vulvovaginitis. A five year old white girl had pus and blood in the urine and an elevated white blood cell count; cystoscopic examination revealed a hemorrhagic cystitis. One six year old colored girl had pyuria and an elevated white blood cell count. Her abdominal pain was due to pyelitis. Three white boys, one four years old and two seven years of age, had ureteral obstruction and hydronephrosis. In one the obstruction was due

TABLE 17. *Incomplete, Unrelated and Incidental Findings*

	NUMBER OF CASES
1. **Incompletely diagnosed and questionable cases:**	
Recurrent cystitis and cord bladder	1
Incomplete visualization of the kidney pelves; work-up refused	1
Cystitis not treated; no pain 11 months later	1
Redundant bowel and kink in the left ureter	1
Question of duodenal ulcer on roentgenogram; improved on dietary management	1
Abnormal duodenal fold pattern	1
After appendectomy, abdominal pain twice with otitis media and once with herpes zoster	1
20–75% eosinophils on stool smear associated with blood eosinophilia; no correlation with symptoms	2
Questionable hepatitis; incomplete follow-up	1
Neurofibromatosis	1
2. **Pathology not related to pain:**	
Aberrant subclavian vessel	1
3. **Incidental findings:**	
Urinary tract anomaly not associated with obstruction or infection	6
Orthostatic albuminuria	2
Nonvisualization of the gallbladder	1
Spina bifida occulta	2

to an aberrant vessel; in the other two the obstruction was due to a ureteral stricture. A 13 year old white girl had an ovarian teratoma. This was first suspected when calcifications were seen in the low abdomen on the intravenous pyelogram films (Fig. 10).

A nine year old colored boy was shown to have mesencyclic fits by the electroencephalogram. He has had no further symptoms since anticonvulsive therapy was instituted.

There were 11 patients in whom the diagnosis was either questionable or incomplete (Table 17). One ten year old colored girl who was treated for recurrent bladder infections had hematomyelia and a cord bladder. The symptoms could not be correlated with the findings. A four year old colored boy had incomplete visualization of the kidney pelves.

Further work-up was refused by the parents. A seven year old white girl had pyuria. No treatment was given, and 11 months later the urine was clear and she was free of symptoms. A 12 year old white girl was shown on roentgenographic studies to have a redundant bowel and a kink in the left ureter. There was associated headache, vomiting and back pain, but no constipation or dysuria. She has had only symptomatic treatment for the headaches and vomiting, and the pain has continued. This child has an intelligence quotient of 69. An eight year old colored boy had a duodenal deformity demonstrated on roentgenogram which was suggestive of an ulcer crater. His symptoms have been controlled with a bland diet. A nine year old colored girl shows an abnormal duodenal fold pattern on the upper gastrointestinal series. Her pain is aggravated by dietary indiscretions. A six year old white boy had recurrent abdominal pain with vomiting over a two year period; an elective appendectomy was done. Four and nine months postoperatively he had abdominal pain associated with otitis media, and 16 months postoperatively he had abdominal pain associated with herpes zoster. There were two patients with 20 to 75 per cent eosinophils shown on smear of the stool; this was associated with eosinophilia in the differential white blood cell count. Allergic work-up was negative in both, and the abdominal pain could not be correlated with the findings. A three year old white girl had abdominal pain associated with light stools and anorexia. The urine was negative for bile; however, the cephalin flocculation and thymol turbidity tests were both 3 +. The stool was positive for occult blood on repeated examinations. One year later the child was asymptomatic, but the laboratory findings remained unchanged. A nine year old white girl had recurrent nocturnal abdominal pain for three years. On physical examination there were widely distributed café au lait spots. A mass developed on the heel during the course of the study. It was excised and on histologic examination was found to be a neurofibroma.

An 11 year old boy was found to have an aberrant subclavian vessel on the upper gastrointestinal films. This finding was interpreted as being a disturbance not related to the abdominal pain complaints (Table 17). Since operative correction, however, his complaints of pain have been less frequent and the pain apparently is less severe.

In 11 patients, abnormalities were found which were believed to be asymptomatic (Table 17). Six patients had urinary tract anomalies without evidence of obstruction or infection. Two patients had orthostatic albuminuria. There was nonvisualization of the gallbladder on repeated attempts in one patient. This is thought to represent a congenital absence of the gallbladder. Two patients were found to have spina bifida occulta on the intravenous pyelogram films.

CONCLUSIONS AND COMMENTS

In a study of abdominal pain in children, Conway[4] found that 10 per cent of the children attending a large out-patient clinic complained of abdominal pain. He attempted to correlate the history with the diagnosis, but was unable to detect any distinctive diagnostic pattern. In this study there was a 5 per cent incidence of serious disorder. Any child complaining of abdominal pain was included, and there was no systematic laboratory investigation utilized.

The present study of long-standing recurrent abdominal pain is based upon the results of readily available laboratory data. In 42 per cent some abnormality was demonstrated, and in 20 per cent the lesion found was responsible for the abdominal pain.

There were six cases of duodenal ulcer proved on roentgenogram findings. The condition was shown to be related to the pain by favorable response to appropriate treatment and roentgen evidence of disappearance of the ulcer crater. In two additional cases abnormality of the duodenal bulb was demonstrated on roentgenograms, and in both the symptoms were relieved by dietary management. This relatively high incidence is in accord with the growing realization that peptic ulcer is not uncommon in childhood. In a report of 254 children with chronic vague abdominal pain, Alexander[1] was able to demonstrate roentgen evidence of duodenal ulcer in 30 cases.

Three patients had ureteral stricture and hydronephrosis demonstrated on intravenous pyelograms and follow-up urograms. The pain of urinary tract obstruction tends to be vague and generalized in children. When the pain is referred to the sympathetic system, associated gastrointestinal complaints can be expected.[3]

Other specific diagnoses related to abdominal pain were small bowel multiple polyposis with recurrent intussusception, appendiceal abscess, hepatitis, ascariasis, vulvovaginitis, cystitis, pyelitis, ovarian teratoma and mesencyclic fits.

The complete blood cell count and urinalysis each disclosed some significant disturbance in 5 per cent of the cases. The stool examination showed an abnormality in 6 per cent, and the abnormality was shown to be related to the complaints in 4 per cent. Although *Enterobius vermicularis* infection was shown to be an incidental finding, a follow-up of the child with ascariasis strongly suggests that, in this case, the infection was responsible for the pain. Gastrointestinal allergy as shown by eosinophils in the stool smear in association with eosinophilia in the differential white blood cell count is frequently accompanied by indefinite abdominal pain.[6] In the two cases studied in this series, however, the findings could not be correlated with the symptoms.

The roentgenographic examinations found to be of value were the

upper gastrointestinal series and the intravenous pyelograms. The upper gastrointestinal series demonstrated some abnormality in 9 per cent of the cases. The lesion was related to the symptoms in 7 per cent. The intravenous pyelogram revealed an abnormality in 14 per cent. Twelve per cent of these were genitourinary anomalies, and 3 per cent caused the abdominal pain by obstruction. Further follow-up of the 9 per cent nonobstructive urinary tract anomalies may later show additional cases in which there is causal relationship. In 153 consecutive autopsies on children, Bigler[2] found an incidence of 13 per cent congenital anomalies of the urinary tract. The finding of 14 per cent in this group is therefore not excessively high.

CASE REPORTS

CASE I. A 13 year old Italian girl has been followed up in the Children's Memorial Outpatient Department since March, 1949, when she was 8 years of age. Her parents

Fig. 11. Barium study of small bowel on July 7, 1950. Arrows point to polyp in small bowel leading an intussusception, shown by the coil-spring appearance of the adjacent small bowel.

brought her to the Clinic because of pallor, anorexia and recurrent abdominal pain of 2 years' duration. The pain was vague, generalized and cramping, occurring 2 or 3 times a week in the late evening, early morning or before lunch. It lasted about an hour, was occasionally accompanied by nausea and vomiting, and was relieved by vomiting or eating.

The history of previous illnesses was not contributory; all other members of her family were in good health.

On physical examination the patient was observed to be a thin, pale, asthenic girl who was not seriously ill. There were no abnormal physical findings.

Laboratory examinations at that time included a complete blood cell count, urinalysis, examination of the stool for blood, roentgen studies of the gastrointestinal tract, and gastric analysis. The only abnormality shown was a moderately severe iron deficiency anemia.

Ferrous sulfate was prescribed, and a normal red blood cell count and hemoglobin were maintained only as long as iron therapy was continued.

Fig. 12. Small bowel barium study on July 22, 1952. Arrows point to polyp in right lower quadrant. No intussusception was present.

Vague abdominal pain continued, and on June 25, 1952, the patient had severe, cramping abdominal pain associated with nausea and vomiting. At that time a firm, slightly tender mass was palpable in the left lower quadrant. A notation was made of small areas of pigmentation on the vermilion border of the lips and on the buccal mucosa. On the intravenous pyelogram films a persistent shadow was interpreted as representing gas in a small bowel loop and suggesting a partial small bowel obstruction.

The pain subsided within a few hours, and the mass decreased rapidly to a small nubbin palpable only intermittently. At exploratory laparotomy on July 10, 1950, a 6-inch ileoileal intussusception was found (Fig. 11). An olive-sized polyp was leading the intussuscipiens. The intussusception was reduced, and a small segment of bowel containing the polyp was resected.

In the following 2 years the patient had occasional episodes of mild abdominal pain, and the blood picture was unchanged by operation. On July 19, 1952, she experienced sudden onset of severe, cramping abdominal pain. There were no abnormal physical findings at that time, and she was admitted to the Hospital on the abdominal pain study.

Laboratory and roentgen examinations were normal except that the urine showed 20 to 30 pus cells per high power field, and the urine culture was positive for Pseudomonas and Aerogenes. Gantrisin was prescribed for the pyuria, and the patient was discharged from the Hospital asymptomatic on July 29, 1952.

There was a recurrence of severe abdominal pain on August 18, 1952. There was slight abdominal tenderness and an intermittently palpable mass in the right lower quadrant. Roentgen examination of the small bowel demonstrated a polypoid defect in a loop of small bowel. Upon review it was noted that this same defect was present in the films of the upper gastrointestinal tract made on July 23, 1952 (Fig. 12).

At laparotomy, on August 21, 1952, an ileoileal intussusception was found with the intussuscipiens led by a small polyp. The distal ileum was inspected and was found to be studded with a multitude of minute, flat sessile polyps. The intussusception was reduced, and a small portion of bowel containing the polyp was resected.

Again on August 11, 1954, a laparotomy was performed because of severe, cramping abdominal pain, and an intussusception secondary to a small bowel polyp was found.

Comment. This girl shows the peculiar pigmentation of the oral mucosa which was first described by Hutchinson[7] in 1896. In addition, she has the associated small bowel multiple polyposis first reported by Weber[7] in 1919 in a follow-up report of Hutchinson's cases. To date, there are 29 proved cases reported in the literature.[5]

CASE II. An 11 year old colored boy was first seen in the Children's Memorial Hospital Outpatient Department on October 4, 1953. He had experienced recurrent

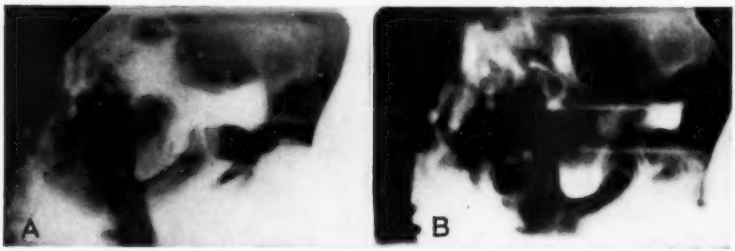


Fig. 13. Barium study of duodenal bulb. *A*, Demonstrates deformed bulb. *B*, Demonstrates the central crater.

"knotlike" upper abdominal pain for one year. It occurred at any time of the day or night and was relieved by eating or by taking soda bicarbonate. There was no nausea or vomiting, and the bowel habit was normal. The pain had become much more severe in the previous 5 days, and his grandmother, suspecting worms, had given him turpentine orally with no relief of symptoms.

His grandmother, who was the only member of his family known to us, had full responsibility for his care. She had suffered from recurrent abdominal pain which did not recur after a cholecystectomy had been performed 2 years previously.

On physical examination this child was found to be slender and fairly well nourished. He appeared to be somewhat apprehensive and expressed concern that he "might have cancer." There were no abnormal physical findings.

He was admitted to this study when he returned to the Outpatient Department on October 21, 1953, again complaining of abdominal pain.

The laboratory examinations revealed normal findings except that the stool was positive for occult blood, and roentgenogram study of the upper gastrointestinal tract

disclosed duodenal deformity and an ulcer crater (Fig. 13). The gastric analysis showed 23.9 degrees free hydrochloric acid and 38.7 degrees total acidity.

Dietary and antispasmodic management was instituted with complete relief of symptoms. Follow-up roentgenograms demonstrate only a residual duodenal deformity.

Comment. There is no characteristic symptom pattern associated with peptic ulcer in childhood. Other patients in this study in whom peptic

Fig. 14. Intravenous pyelogram. The right kidney fails to visualize. The left kidney is normal.

ulcer could not be demonstrated gave histories far more suggestive than that of this boy.

CASE III. A 7 year old white boy was brought to the Children's Memorial Outpatient Department by his mother on March 6, 1953, because of abdominal pain and vomiting. Constipation and fecal soiling had been present since infancy. Although his daytime bladder control was good, he had almost nightly enuresis. For the previous 2½ years, he had experienced attacks of abdominal pain associated with nausea and vomiting. The attacks occurred about every 2 months, and each attack lasted 3 to 4 days. During these episodes, attempts to eat or drink resulted in vomiting; he was comfortable only when lying quietly in bed.

He was hospitalized elsewhere in February, 1952, for treatment of severe dehydration. Again in August, 1952, he was hospitalized because of severe abdominal pain and persistent vomiting. Roentgen studies of the gastrointestinal tract showed no abnormality. His mother stated that he was a very nervous child, and that these attacks occurred after emotional upsets.

The family history was not contributory.

On physical examination he was found to be a pale and lethargic, but not acutely ill boy. There were no specific abnormal findings.

Laboratory investigation for recurrent abdominal pain was done. The results of

the studies were negative except for a 1+ albumin in the routine urinalysis and non-visualization of the right kidney on intravenous pyelogram (Fig. 14).

On retrograde pyelography a hydronephrosis secondary to an aberrant vessel was found (Fig. 15). A nephrectomy was performed, and the patient has had complete relief of all symptoms since operation.

Fig. 15. Retrograde pyelogram. Hydronephrosis present on the right, which was caused by an aberrant vessel at the ureteropelvic junction.

Comment. This case exemplifies the vagueness of the pain associated with urinary tract obstructions in childhood, and the prominence which gastrointestinal symptoms may assume.

SUMMARY

1. A review of the essential elementary points in history taking and physical examination in children has been made.

2. A classification of causes of abdominal pain has been given.

3. An analysis has been made of 95 children with chronic abdominal pain, showing the incidence of pathology and the relative importance of various diagnostic procedures.

4. Case histories demonstrating the use and interpretation of roentgenographic studies have been presented.

REFERENCES

1. Alexander, F. K.: Duodenal Ulcer in Children. Radiology, 56:799, 1951.
2. Bigler, J. A.: Anomalies of the Urinary Tract in Children. J.A.D.C., 38:960, 1929.

3. Campbell, M.: Clinical Pediatric Urology. Philadelphia, W. B. Saunders Company, 1951, p. 142.
4. Conway, D. J. A Study of Abdominal Pain in Children. Great Ormond St. J., 2:99, 1951.
5. Editorial: Intestinal Polyposis with Melanin Spots of Oral Mucosa, Lips, and Fingers. J.A.M.A., *155*:1063, 1954.
6. Hoefer, P. F. A., Cohen, S. M., and Gruley, D. McL.: Paroxysmal Abdominal Pain. J.A.M.A., *147*:1, 1951.
7. Jeghers, H., McKusick, V. A., and Katz, K. H.: Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips and Digits: A Syndrome of Diagnostic Significance. New England J. Med., *241*:933, 1031, 1949.

700 North Michigan Avenue
Chicago, Illinois (Dr. Hardy)

THE ETIOLOGY OF VOMITING IN INFANCY AND CHILDHOOD

JAMES G. HUGHES, M.D.

Vomiting is one of the most common and important symptoms in pediatric practice. Frequently it is caused by temporary and trivial conditions in which the etiology is self-evident. In other instances it is of serious portent, its etiology is more obscure, and careful studies are necessary in order to establish its cause.

Usually vomiting causes insignificant metabolic disturbances, but when persistent and severe it has a profound effect, producing marked alterations of fluid and electrolyte balance, impairment of renal function, ketosis, and destruction of tissue through starvation. Furthermore, vomiting predisposes to a variety of undesirable complications such as otitis media, pneumonia, atelectasis, or asphyxiation due to aspiration of vomitus. Therefore it is important to ascertain and correct the cause of vomiting as quickly as possible.

In this presentation, not intended to be encyclopedic, I shall stress etiology and differential diagnosis more than treatment, and emphasize neonatal emesis.

BASIC INFORMATION NECESSARY FOR ETIOLOGIC DIAGNOSIS

When vomiting is easily explained by some obvious condition, full-scale evaluation according to the following principles is scarcely indicated. In the many instances in which the cause is not apparent, however, nothing short of a thorough approach is warranted. This involves

From the Division of Pediatrics, University of Tennessee, and the John Gaston and Le Bonheur Children's Hospitals, Memphis, Tennessee.

a definite plan of action. The quest for the elusive diagnosis then becomes an interesting chase.

When the cause of vomiting is not readily apparent, careful evaluation of the following items is indicated: (1) age of patient; (2) character of vomitus; (3) frequency of vomiting; (4) force of vomiting; (5) duration of vomiting; (6) timing of emesis in relation to feedings or mealtime; (7) character of feedings; (8) feeding methods; (9) careful history to determine the presence of conditions that might explain vomiting; (10) physical examination; (11) laboratory studies; (12) roentgenographic procedures.

Age of Patient

Consideration of the age of the patient often narrows diagnostic possibilities.

The clearest division is between vomiting in the newborn period and subsequent emesis. In newborn infants (birth to one month of age) emesis is usually due to material swallowed during labor and delivery, intracranial injury, congenital obstructions of the alimentary tract, faulty feeding methods or improper composition of the formula. It is less often due to acute infections and allergy.

During the remainder of the first year, vomiting as a result of stenosis or compression of the alimentary tract may first make its appearance, but emesis during this period is more commonly due to faulty feeding methods, improper composition of formulas, enteral and parenteral infections, or allergy to milk or other foods.

After the first year, feeding methods are less often to blame, but enteral and parenteral infections remain prominent causes. Psychogenic vomiting becomes more important after the second year, as does recurrent (cyclic) vomiting. During this period other causes make their appearance with increasing frequency, such as emesis due to intra-abdominal inflammation—for example, appendicitis and mesenteric adenitis—or vomiting due to infection in the urinary tract, especially when associated with obstructive uropathies.

There are numerous examples of emesis that have no particular age incidence, but in many instances consideration of age does facilitate etiologic diagnosis.

Character of Vomitus

Important points concerning the character of the vomitus are (*a*) whether it is curdled and sour, implying that the food entered the stomach; (*b*) whether it contains unaltered food, indicating that it has not reached the stomach, or has remained there only briefly; (*c*)

whether it contains bile, implying that the vomitus, at least in part, is originating below the ampulla of Vater; (*d*) whether it contains blood, which usually means active hemorrhage, but in the newborn infant may represent blood swallowed during delivery or derived afterwards from a fissured nipple; (*d*) odor, especially whether fecal in character, caused by persistent low-lying obstruction; (*e*) quantity of material vomited, an indication of probable extent of fluid and electrolyte depletion.

Frequency of Vomiting

Frequent vomiting indicates persistence of the causative factor, entails greater loss of fluid and electrolytes, and tends to produce malnutrition.

Force of Vomiting

One should differentiate between regurgitation, in which the vomitus spills from the mouth as from a cup, and forceful vomiting, in which it is projected explosively. Regurgitation is usually due to improper feeding techniques, to habitual regurgitation (rumination), and less often to cardioesophageal relaxation (chalasia). More rarely it may be associated with cardioesophageal spasm (achalasia), diverticulum of the esophagus, stenosis of the esophagus or marked compression of the esophagus by an aberrant great blood vessel.

Forceful vomiting always suggests obstruction, especially in newborn babies, made evident if abdominal distention and failure to pass meconium are present. Most vomiting after one year of age is forceful and due to a wide variety of causes discussed later.

Duration of Vomiting

Vomiting that occurs once or twice within a period of a few hours and then ceases implies a temporary cause, particularly onset of acute infection. Recurrent vomiting indicates continuation of the causative factor and calls for greater study of a long list of possibilities. Furthermore, the degree of metabolic derangement is apt to be much more severe in persistent vomiting as contrasted to occasional emesis.

Relationship to Feedings

Determining the relationship to feedings is often of much help in diagnosis. In infancy, vomiting occurring during or immediately after a feeding is almost always due to faulty feeding methods, chiefly gastric overdistention with air and milk. Dysphagia associated with regurgita-

tion of unaltered food implies an esophageal cause of emesis. Inability to take normal quantities of food and associated with emesis soon after feeding suggests diminution of gastric capacity, as from diaphragmatic hernia in which the stomach is in the thorax, or, rarely, such lesions as gastric bezoar or duplication of the stomach. We have noted vomiting to occur soon after feedings and to be preceded by upper abdominal distention and a sense of unusual fullness in some patients with duodenal compression caused by peritoneal bands associated with malrotation of the colon. After infancy, psychologic tension at mealtimes is a fairly frequent cause of vomiting.

Character and Quantity of Feedings

Under this heading fall excessively dilute feedings which produce gastric distention, unduly concentrated formulas, formulas too high in fat content, and acid milk formulas given to certain babies who tolerate them poorly. Of special importance is the fact that infants who have had severe infections, especially gastroenteritis, regain tolerance for formulas of average strength only slowly and may vomit if food intake is increased too rapidly. Formulas prepared from milk that has been frozen may cause emesis.

Feeding Methods

Improper feeding techniques leading to overdistention of the stomach, particularly by air swallowing, is an especially frequent cause of emesis in young infants, and will be discussed in more detail later.

Failure to warm the formula may produce vomiting, although some infants strangely prefer cold feedings.

At any age hurried eating may cause vomiting, particularly when the child is fatigued, overheated or excited.

History to Determine Causative Conditions

Circumstances associated with emesis may readily explain its etiology. Examples are (*a*) vomiting associated with fever, implying infection as the cause; (*b*) fever, vomiting and abdominal pain, suggesting such entities as appendicitis, mesenteric adenitis, acute infectious hepatitis, the "abdominal crisis" of sickle cell disease, diabetic acidosis or pyelonephritis; (*c*) sudden agonizing pain in a previously well young infant, followed by vomiting, suggesting intussusception; (*d*) head trauma, vomiting being caused by fright, cerebral edema or hemorrhage; (*e*) group vomiting of children who have eaten a common meal, implying food poisoning as a possibility; (*f*) vomiting from fright by a child to

whom a physician represents the demon incarnate; (*g*) the medically embarrassing emesis resulting from pressure on a full stomach while palpating for the spleen. Many other examples will occur to the reader. The point is that one must look beyond the stomach in every case of vomiting.

Physical Examination

Physical examination often helps determine the cause of vomiting, such as finding acute tonsillitis, palpating a pyloric tumor or the mass of intussusception, or observing generalized abdominal distention and tenderness with lack of peristalsis in peritonitis. Furthermore, physical examination helps reveal the extent of physiologic disturbance induced by vomiting, such as detecting dehydration, malnutrition, acetone odor of the breath, deep pauseless Kussmaul respiration of acidosis, or the shallow irregular respiration of alkalosis when the vomitus consists largely of gastric contents.

Laboratory Data

Laboratory studies are indicated if the child is acutely ill, or vomiting is recurrent, or some obviously simple explanation of emesis is not apparent. Routine examination of blood and urine may help in diagnosis. More severe cases of vomiting may profit by determination of serum chloride level, plasma carbon dioxide content, blood nonprotein nitrogen, or hematocrit. The extent to which other laboratory information is needed depends upon the nature of the case.

Roentgenographic Studies

X-ray studies may be of value in many conditions producing vomiting, chiefly those in which some degree of obstruction exists. A plain roentgenogram without contrast media may be all that is indicated, as in complete obstruction of the bowel in newborn infants. In other instances careful studies with radiopaque contrast media are required.

VOMITING IN THE NEWBORN INFANT

Vomiting in newborn infants is usually due to (1) gastric irritation from material swallowed during delivery; (2) intracranial conditions; (3) faulty feeding methods or improper composition of feedings; (4) acute infections; (5) most importantly, congenital anomalies of the alimentary tract.

Gastric Irritation

Blood, meconium or other irritating material may be swallowed during delivery and produce vomiting in the first day or two through gastric irritation. Lavaging the stomach ordinarily suffices to correct such emesis.

Vomiting of blood by a newborn infant is of special interest, since the blood may be the result of hemorrhage from the baby, or may merely represent blood swallowed during delivery or derived from nursing a breast that has a fissured nipple. Blood swallowed during delivery is vomited on the first day, as a rule. Since it usually takes several days for a nipple to become fissured, vomiting of blood obtained from this source usually does not occur until several days or a week after delivery. Causes of hemorrhage with hematemesis in the early newborn period include sepsis; hemorrhagic disease of the newborn due to hypoprothrombinemia, usually occurring on the second to fifth day and often accompanied by bleeding from other sources; and rarely peptic ulcer. Prolonged administration of broad-spectrum antibiotics without concomitant use of vitamin K may result in hematemesis from hypoprothrombinemia, as may hepatitis in newborn infants.

If there is doubt whether the blood represents hemorrhage or only swallowed blood, the blood in the vomitus can be tested by the alkaline denaturation procedure to determine whether it contains adult or fetal type hemoglobin. Fetal hemoglobin (from hemorrhage) resists alkaline denaturation, whereas adult type hemoglobin (from swallowed blood) does not.

Intracranial Conditions

Intracranial hemorrhage, cerebral edema or hypoxia of the brain may all produce emesis. Subdural hematoma originating from the trauma of delivery may also produce vomiting, but often has not achieved sufficient size in the first days to do so. Anomalies of the brain, especially internal hydrocephalus, may produce vomiting in the neonatal period. I have seen osteopetrosis (marble bones) cause increased intracranial pressure with neonatal emesis. Meningitis is a rare cause of vomiting in this period.

Feeding Methods and Composition of Food

With the exception of feeding too much or too fast, faulty technique in feeding infants, leading to vomiting, consists almost entirely in permitting large amounts of air to enter the stomach and failure to remove the air by bubbling the infant. The harsh word "belch" is seldom used

in practice, being supplanted by the easily understood and more euphemistic term "bubbling the baby."

The causes of gastric distention with air are (1) prolonged nursing at a breast devoid of milk, air swallowing occurring and resulting in overdistention; (2) nursing from a bottle the nipple of which has holes so small that the milk does not flow freely, again resulting in air swallowing; (3) failure to hold the baby in a semi-upright position during nursing, thus preventing eructation of air during the feeding; (4) failure to "bubble" the baby after the feeding to permit eructation of air; (5) air swallowing by a hungry baby who sucks his fingers and fists between feedings and cries excessively. If one watches such babies closely, or rather listens to them attentively, he will often note a bolus of air go down with a gulp. How to correct these faulty techniques is of course self-evident.

Improper composition of the formula has already been discussed.

Acute Infections

When the cause of vomiting in a newborn infant cannot be clearly explained, one should always suspect infection, such as sepsis, pneumonia or urinary tract infection, frequently associated with an obstructive anomaly. Infectious diarrhea in newborn infants often causes vomiting. Meningitis has been mentioned as a rare cause.

Congenital Anomalies of the Alimentary Tract

Early onset of vomiting in newborn infants, especially on the first day of life, suggests the possibility of a congenital anomaly of the alimentary tract, particularly if abdominal distention develops and there is failure to pass meconium. Early diagnosis is highly important because of the hazards of emesis previously mentioned. Newborn infants have narrow fluid and electrolyte reserves and quickly suffer dehydration and acidosis when emesis is protracted. Furthermore, progressively distended bowel becomes devitalized, leading to sepsis or peritonitis, through either ulceration or perforation.

Atresia of the Esophagus. In the usual type the upper segment of the esophagus ends as a blind pouch, and the lower connects with the trachea through a fistula near the bifurcation. Such infants cannot swallow saliva and secretions, and the first indication that atresia is present is the increased amount of secretions in the mouth, possibly necessitating suction. Unfortunately, nursery personnel and physicians are often not alert to the meaning of this finding. When the first feeding, glucose solution, is given, the infant takes one or two swallows, fills the upper blind esophageal pouch, and as the fluid spills over into

the lungs, chokes, coughs and may turn cyanotic. Even then, if one is unfamiliar with the condition, atresia may not be suspected, but at each successive feeding the "cup runneth over." Soon someone suspects the diagnosis, which is then proved by inability to pass a catheter into the stomach and by instillation of 2 cc. of iodized oil into the upper blind pouch. Fluoroscopy or a plain roentgenogram reveals air in the intestines because of the fistula between the trachea and the lower esophageal segment.

Unfortunately, days sometimes elapse before a correct diagnosis is made, the infant being treated possibly for atelectasis or pneumonia that really results from repeated aspiration. I once saw a baby with atresia who was 12 days old and getting along quite well with parenteral fluid and electrolyte therapy and antibiotic treatment for atelectasis. Primary esophageal anastomosis was performed, and he survived. He was the exception to the established rule that the earlier the diagnosis is made, the greater the chance for recovery after operation. When the diagnosis is not made early, pneumonia seriously handicaps chances of survival.

I shall not discuss all the variations of esophageal atresia, but I should like to describe a most interesting case of neonatal vomiting based on tracheo-esophageal fistula without atresia.

A newborn infant swallowed well, but almost invariably vomited soon afterwards, and it was noted that upper abdominal distention was almost constantly present. An esophagram with iodized oil seemed normal, and even in the prone position no fistula between the esophagus and trachea could be demonstrated. However, esophagoscopy revealed the rushing of air from the trachea to the esophagus on each inspiration. This led to gastric distention and vomiting. The baby was placed in the prone position, methylene blue was instilled into the esophagus, and bronchoscopy was performed immediately. No methylene blue was seen in the larynx, but it was detected in the trachea, proving the presence of a fistula. Operation revealed the fistula, which was closed, and the infant recovered. In this case feedings did not initiate coughing, since the fistula was so small that food did not pass through it, but air did.

Achalasia and Chalasia. Achalasia (cardioesophageal spasm) may interfere with entrance of food into the stomach and cause dysphagia and regurgitation of unchanged milk, associated with coughing from aspiration of the food. Chalasia (relaxation of the cardia) may cause regurgitation when the infant is lying down, but not when he is kept propped up in a sitting position after feedings. Both conditions are easily proved by esophagrams.

Esophageal Diverticulum. This is an extremely rare cause of regurgitation of unchanged food.

Diaphragmatic Hernia. Herniation of the stomach into the thoracic cavity usually produces symptoms in the newborn period, but may be asymptomatic. Vomiting occurs soon after food intake. Rapid respira-

tion and cyanosis due to pulmonary compression are usually present. The herniation is ordinarily into the left hemithorax. The affected side of the chest moves less freely with inspiration, is more often dull than hyperresonant to percussion, the heart is pushed toward the opposite side, and one may or may not hear peristaltic gurgling sounds through the chest wall. A plain roentgenogram proves the diagnosis.

Duplication of the Stomach. The rare condition of duplication of the stomach, of which we have seen two cases, may produce vomiting through diminution of gastric capacity.

Pyloric Stenosis. In pyloric stenosis vomiting usually begins in the second or third week, but may start in the first. Emesis becomes progressively more frequent and forceful, bile is practically never present in the vomitus, and visible peristaltic waves are seen. Owing to persistent vomiting, stools are small and passed infrequently. First, the baby fails to gain weight, then loses, dehydration occurs, oliguria is noted, and in advanced cases shallow, irregular respiration with perhaps periods of apnea heralds the presence of alkalosis. The pyloric tumor can usually be palpated, especially if the infant is examined in three positions: (1) supine, (2) prone, (3) held in a sitting position, the fingers of the examiner being pressed into the abdomen as the baby is made to lean forward. Examination immediately after the infant vomits may facilitate palpation of the tumor.

Roentgenographic studies are not required if the tumor is felt, but may aid in diagnosis if it is not. A small amount of iodized oil, no more than 10 cc., is administered, and the infant is examined carefully in the right anterior oblique position. Delay in emptying time may be noted, but is far less significant than the finding of a narrow, elongated pyloric canal (string sign) and crescentic deformities of the duodenal cap caused by the rounded pyloric tumor bulging into the duodenum.

Chief errors in roentgenographic technique are (1) administration of barium instead of iodized oil, which may result in aspiration when the barium is vomited, causing barium pneumonitis; (2) depending on delayed emptying time alone as the only criterion of diagnosis; (3) failure to examine in the right anterior oblique position to see the string sign and crescentic deformities of the duodenal cap.

Best American opinion counsels supportive preparation, especially correction of dehydration, alkalosis, and possibly anemia, hypoproteinemia and hypokalemia, followed by operation. So-called medical management is not advised, except to restore the patient to a condition suitable for operation.

Pylorospasm is a condition simulating pyloric stenosis in regard to frequent, forceful vomiting and perhaps visible peristalsis, but a tumor cannot be felt, the stools are more normal, roentgenography does not

reveal evidence of pyloric stenosis, and so-called medical management (thickened feedings, mild sedation and perhaps atropine or similar drugs) relieves the difficulty.

Duodenal Obstruction. Duodenal obstruction leading to vomiting is of four main types: (1) atresia, or complete obstruction by an intraluminal diaphragm; (2) congenital stenosis; (3) compression of the duodenum in malrotation of the colon; (4) encirclement of the duodenum by an annular pancreas.

DUODENAL ATRESIA. The atresia or diaphragmatic band is usually in the third portion of the duodenum. High intestinal obstruction occurs, upper abdominal distention may be noted, and vomiting begins within the first 24 hours after delivery. The vomitus contains bile. A plain roentgenogram of the abdomen reveals a "double bubble" sign due to distention of the stomach and the proximal portion of the duodenum. It is a waste of time to use opaque media; if barium is used, vomiting and aspiration may result in barium pneumonitis. Early operation is required.

STENOSIS. Congenital stenosis of the duodenum may cause neonatal vomiting. The obstruction is not complete, stools are passed, the roentgenogram reveals gas in the bowel distal to the obstruction, and fluoroscopy with iodized oil may show the area of constriction. Treatment is surgical.

MALROTATION OF THE COLON. Malrotation of the colon may produce duodenal obstruction in two ways: (*a*) The cecum may be in the right upper quadrant, attached to the posterolateral abdominal wall by peritoneal bands that cross and compress the duodenum. We have seen several such babies in the past few years who had complete intestinal obstruction in the newborn period and were clinically indistinguishable from cases of duodenal atresia. Barium enema proves malrotation to be present, leading to accurate preoperative diagnosis. Division of the bands at operation is corrective. (*b*) The cecum may be anchored high in the right upper abdominal area and the duodenum may be compressed by the weight of the cecum, rather than by bands. Freeing the cecum from its abnormal location relieves the compression.

ANNULAR PANCREAS. In the past few years we have seen five babies in whom annular pancreas produced duodenal obstruction in the newborn period. In this condition the head of the pancreas encircles the duodenum and compresses it. Clinically, the patient's course closely resembles that of a baby with duodenal atresia or compression of the duodenum by malrotation of the colon. It is our impression that most of these babies do not vomit bile. The plain roentgenogram of the abdomen again reveals the "double bubble" sign. If iodized oil is instilled into the stomach, a characteristic deformity of the duodenum will be noted at the site of constriction by the annular pancreas. Operation

consists in establishing a by-passing anastomosis. Division of the encircling pancreatic tissue, which has a duct system of its own, may lead to formation of a fistula, pancreatitis or subsequent cicatricial stenosis with persistence of symptoms.

Atresia or Stenosis in Other Parts of the Small Bowel. Atresia or stenosis may occur in the jejunum, ileum, colon or rectum and give rise to intestinal obstruction in the newborn period. It is easy to diagnose the presence of obstruction in these cases, but more difficult to ascertain by roentgenography the location of the obstruction. This is an academic point, however, since operation is mandatory.

In the differential diagnosis of atresia versus stenosis of the intestinal tract in the newborn, I have never felt that Farber's test was necessary. This test consists in the demonstration of cornified epithelial cells in the meconium of infants with a patent alimentary tract and their absence in infants with atresia. The cells originate from the fetal skin, are exfoliated into the amniotic fluid, and are swallowed with the fluid. All patients with atresia will quickly exhibit incontrovertible evidence of obstruction, making laparotomy mandatory. Those in whom stenosis is so severe as to mock atresia also require exploration. Although the test represents a nice observation, it is actually of only academic interest.

Volvulus. In malrotation of the colon an associated abnormality is an unusually short posterior attachment of the mesentery of the small bowel, which arises as a slender stalk and spreads out like a Japanese fan, fostering twisting and strangulation of the blood supply of the small intestine. Symptoms are sudden onset of obstruction with severe abdominal distention, vomiting, constipation, fever, and shock if the condition is not corrected. Strangulation and gangrene of the bowel occur rapidly if the condition is not quickly detected and relieved surgically. The danger of this entity is that it may be confused with obstruction on the basis of atresia or stenosis, lesions that do not aggressively impair blood supply to the bowel. Hence the need for immediate operation may not be appreciated, and fatal delay may ensue. The possibility that an obstruction in a newborn infant may be due to volvulus, though rare at this period of life, is one of the factors that demand immediate exploration of newborn infants who have complete obstruction.

Functional Intestinal Obstruction. Zuelzer and Wilson[9] have called attention to intestinal obstruction in the newborn period due to absence of the intramural myenteric plexus in the lower colon and rectum, but at times even in the small bowel. These cases are now regarded as instances of aganglionic megacolon with first obstructive manifestations in the newborn period. A familial tendency has been noted. In aganglionic areas there is functional constriction of the bowel and impairment

of peristaltic propulsive activity. The proximal portion of the bowel, containing the plexus cells, dilates, and the wall eventually hypertrophies as it works against the functional obstruction. Newborn infants with this condition have constipation, abdominal distention and vomiting. Roentgenograms resemble those of patients with organic obstruction of the distal ileum or colon. When laparotomy is performed, no organic obstruction is noted, but there is massive dilatation of the colon and possibly the lower portion of the small bowel, with diminution of caliber of the bowel immediately distal to the dilated area. In severe cases, if colostomy or ileostomy is not performed, these newborn babies usually die. Such procedures permit maintenance of existence until definitive removal of the aganglionic portion can be accomplished, as in the Swenson "pull-through" operation.

Meconium Ileus. The first manifestation of cystic fibrosis of the pancreas (mucoviscidosis) may be meconium ileus, a condition in which decrease of pancreatic enzymatic activity results in meconium which is sticky, tenacious and drier than normal, therefore difficult to propel by peristaltic activity. There is failure to pass meconium, or laborious passage of only a few mucilaginous stools. Abdominal distention and vomiting occur, usually on the first day of life. Palpation may yield a doughy sensation as one feels the intestines clogged with meconium. A plain roentgenogram may reveal a stippled appearance of the affected areas of the bowel. There is a great tendency to perforation, which may occur prenatally or within a few days after delivery. If this has occurred, the roentgenogram will reveal flecks of calcium in the peritoneal cavity. Immediate operation is advisable. In some instances the thick meconium can be manually removed by opening the bowel, or irrigating with a solution of saline. In other cases the best procedure is a double-barreled ileostomy, followed by irrigations of pancreatin solution.

Malformation of the Rectum. The initial examination of the newborn infant should include inspection for presence of an anus, but the obvious abnormality of anal atresia is occasionally unnoticed until the nurse discovers it when attempting to take the infant's temperature, or when the baby fails to pass a stool. Atresia may be located higher in the rectum, necessitating digital examination in an infant presenting signs of intestinal obstruction in the neonatal period. It would be indeed an embarrassing error, and harmful to the infant, to explore the abdominal cavity for the site of obstruction, only to find that it could have been detected by an inquisitive finger.

Adrenocortical Insufficiency. Newborn infants with adrenocortical insufficiency frequently vomit, at times projectilely. Indeed, some of these patients have been operated upon with the mistaken diagnosis of pyloric stenosis.

If the infant is a girl, pseudohermaphrodism may be present, the clitoris being enlarged to such an extent that the uninitiated may think he is dealing with a male infant with hypospadias. If the baby is a boy, the penis may or may not be noticeably enlarged, and the scrotum may or may not be somewhat pigmented.

There is excessive elaboration of androgens and deficient production of the electrolyte-controlling hormone and, at times, the carbohydrate-regulating hormone.

For the first few days or week the infant may do well, but then there is failure to gain, followed by rapid onset of dehydration and weight loss, associated often with vomiting and possibly diarrhea. Attempts to hydrate the baby are often unsuccessful, owing to inability to reabsorb sodium chloride and water in the proximal tubule. Despite administration of normally adequate fluid intake, dehydration recurs, like a leaky bucket losing water. Inability to hydrate the infant satisfactorily soon attracts attention to the abnormally large urinary output, the cause of the dehydration. Hypoglycemic attacks may occur.

Blood chemical studies help establish the diagnosis. Owing to abnormal loss of base in the urine, and severe dehydration, acidosis is present, the carbon dioxide-combining power often being in the range of 25 to 30 volumes per cent. Plasma sodium is low, chloride may be low, potassium may be increased, and the hematocrit and blood nonprotein nitrogen are elevated. Twenty-four hour urinary output of 17-ketosteroids is usually increased.

Treatment consists in addition of sodium chloride to the formula, injection or implantation of desoxycorticosterone acetate (DOCA), and the subsequent administration of cortisone if indicated to suppress excessive androgenic output.

The condition is readily differentiated from pyloric stenosis by the following points: in pyloric stenosis urinary output is decreased, it is not abnormally difficult to hydrate the patient, metabolic alkalosis with increased carbon dioxide content is present, a tumor may be felt, and roentgenograms may reveal the "string sign" and crescentic duodenal deformities.

VOMITING AFTER THE NEONATAL PERIOD

The group of conditions that occasion emesis after the neonatal period is more difficult to diagnose, since one is rarely assisted by characteristic age incidence, as in many types of vomiting in the newborn infant. There is, however, generally a definitely observable condition that adequately explains emesis. We look more to the bowel for the cause of vomiting in the first month and more to the rest of the body afterward.

Rumination (Habitual Regurgitation)

Many infants regurgitate small quantities of milk from time to time throughout the day, especially when leaning forward, when picked up or even while lying quietly. The milk is sour and curdled. Such infants usually thrive in spite of regurgitation, but are socially unacceptable because of unpredictable emesis. Bubbling the baby during and after feedings, placing him on his right side after feedings, and perhaps the use of thickened formulas may minimize such regurgitation.

Other infants appear to initiate emesis deliberately, the prelude to regurgitation consisting in grimacing, frowning, moving the mandible forward and backward, stiffening the body, arching the back, and finally expelling the food. Some even thrust fingers into the mouth to begin the act. Esophagrams are usually normal, ruling out cardioesophageal relaxation (chalasia), cardioesophageal spasm (achalasia), diverticulum of the esophagus or congenitally short esophagus.

Thickened feedings often diminish the frequency of regurgitation, or prevent it altogether. If the fingers are thrust into the mouth to initiate regurgitation, elbow restraints can be used. I do not believe that it is safe to use a chin strap to prevent the food from being regurgitated, as has been recommended by some. There is danger of aspiration of food if this is done. No matter how troublesome a condition, treatment should never be more dangerous than the disease we treat.

Vomiting Due to Enteral Infection

Vomiting due to gastroenteritis is a common cause of emesis in young infants, especially in certain parts of the country where enteral infections are more prevalent. The fact that diarrhea is an associated symptom, often the dominant one, clarifies the cause of such vomiting.

Vomiting Due to Parenteral Infection

One of the most frequent causes of emesis in infants past one month of age is parenteral infection, usually in the upper respiratory tract. The previously healthy child wilts and droops, becomes irritable, has anorexia, and then suddenly vomits, perhaps hours before fever and evident pharyngitis appear. Emesis usually occurs only once or twice at onset of infection, but may persist and become the dominant clinical feature, outranking the infection itself in importance.

Abdominal Conditions

A great variety of abdominal conditions may cause emesis.

Appendicitis. Although rare under two years of age, acute appendicitis advances in frequency as the years progress and must always be

regarded as the possible cause of vomiting in a child who also has abdominal pain and fever.

Peritonitis. Acute peritonitis is usually secondary to appendicitis, but may be caused by bacteremia (especially in nephrotic children), perforation of a peptic ulcer, perforation due to complete intestinal obstruction in the newborn (atresia, meconium ileus, volvulus, and so on) or traumatic rupture of the intestine. Abdominal pain, vomiting, distention, constipation and fever are the main symptoms. I have seen one case in the newborn due to perforation of the transverse colon at two sites where the muscularis was defective.

Mesenteric Adenitis. Mesenteric adenitis, usually associated with throat infection, is also a frequent cause of vomiting, abdominal pain, and fever. Clinically, it may closely mock appendicitis, but the pain and tenderness are usually more diffuse. I have no confidence in the opinion, held by some, that in mesenteric adenitis the tenderness is on the right when the child lies on his right side and on the left when he is on his left side. It sounds plausible that there would be a shift of the mesenteric glands with change of position, but this is not borne out with sufficient regularity to be a dependable sign.

Meckel's Diverticulum. A Meckel's diverticulum may become inflamed, and the resultant diverticulitis may be clinically indistinguishable from acute appendicitis, producing fever, abdominal pain, and vomiting.

Intussusception. Vomiting associated with sudden onset of agonizing abdominal pain in a previously healthy young infant, usually in a male, suggests the presence of acute intussusception. The pain recurs in intense paroxysms, a mass is felt in the abdomen, and "currant jelly" stools containing blood and mucus may be passed.

Peptic Ulcer. Vomiting may be a symptom of peptic ulcer, and blood may be in the vomitus. In infancy, ulcers may occur as isolated phenomena, or in association with septicemia, severe gastroenteritis, burns (Curling's ulcer) or brain lesions (Cushing-Rokitansky ulcers). In childhood they are more often primary and tend to occur in psychologically maladjusted children. Epigastric or paraumbilical pain may occur a few hours after mealtime and be relieved by eating. Melena may be noted. Roentgenography may or may not reveal characteristic findings. Medical management, similar to that afforded adults with peptic ulcers, and including careful psychologic evaluation and therapy, usually suffices. Operation is required in only a minority of patients.

Hepatitis. Acute hepatitis frequently produces repeated vomiting and moderate to rather severe upper abdominal pain at onset of the disease. Such manifestations may be present before icterus is obvious, but generally disappear within a few days.

Intestinal Obstruction. After the first month of life intestinal obstruc-

tion is more often due to inflammation within the abdominal cavity than to mechanical factors. However, congenital anomalies that did not produce symptoms in the first weeks may cause obstruction at a later date, frequently of an intermittent type. This may occur in such conditions as malrotation of the colon or mild to moderate intestinal stenosis. Vomiting and abdominal distention are prominent symptoms.

Vomiting due to incarceration of inguinal hernias is by no means rare. The dangers of strangulation are so real and operation so safe that it is recommended that inguinal hernias be repaired surgically rather than managed by trusses.

Urinary Tract

Vomiting frequently occurs in association with pyelonephritis. In young infants this may be of such degree as to simulate pyloric stenosis. Congenital obstructive uropathies associated with urinary tract infection often produce vomiting and perhaps attacks of abdominal pain. When the cause of recurrent abdominal pain, with or without concomitant emesis, is unexplained, it is a wise procedure to obtain excretory urograms. In severe renal insufficiency, either acute or chronic, vomiting is frequently an outstanding symptom. Urinalysis, with particular reference to low specific gravity and abnormal elements in the urine, and determination of the blood nonprotein nitrogen value are of help in detecting such cases.

"Abdominal Epilepsy"

Recurrent attacks of severe abdominal pain associated with vomiting and not otherwise explained should attract attention to the possibility of "abdominal epilepsy" and lead to the taking of an electroencephalogram. Dilantin may prove effective in such cases.

Intracranial Conditions

A wide variety of intracranial conditions initiate emesis. These include various cerebral infections, neoplasms, hemorrhage, toxins, and congenital abnormalities of the brain.

In acute bacterial meningitis emesis is an early and often persistent symptom. The same is true of the various forms of encephalitis.

Brain tumors produce vomiting which is often projectile and associated with change of position. Nausea may or may not accompany the vomiting. Recurrent severe headache is often characteristic, and there may be disturbances of vision and instability of gait. Detailed neurologic studies, roentgenography and special neurosurgical procedures establish the diagnosis.

Intracranial hemorrhage from trauma or rupture of a congenital aneurysm may cause emesis. The aggressive expansion of a subdural hematoma is a notorious cause of vomiting and should be thought of as a possibility in infants with emesis whose heads enlarge more rapidly than normal, who may have persistent bulging of the anterior fontanel, and who may reveal neurologic abnormalities, including spasticity or convulsions.

Head trauma may produce vomiting, not only because of the resulting cerebral edema or hemorrhage, but also from the emotional stress of fright.

Lead poisoning produces intense cerebral edema and persistent vomiting associated with papilledema, recurrent convulsions, excess protein and cells in the cerebrospinal fluid, and lead lines in roentgenograms of the long bones.

Endocrine Conditions

Endocrine abnormalities may produce vomiting. Vomiting frequently occurs in diabetic acidosis. Vomiting that occurs several hours after a meal, or before breakfast, suggests the possibility of hypoglycemia, especially if associated symptoms are hunger, weakness, tremulousness, irritability and mental confusion. Hypoglycemia would obviously be entertained as a possible cause of emesis in a child taking insulin. The crisis of hyperthyroidism is characterized by vomiting, diarrhea, fever and increasing prostration.

Epidemic Vomiting

In recent years epidemics of nausea and vomiting have occurred, thought to be on the basis of a viral infection, and affecting adults as well as children. Some patients have nausea, vomiting, diarrhea, abdominal pain, headache, slight elevation of temperature and often moderate pharyngeal hyperemia. The condition is more severe in children, who may have explosive onset of vomiting. Adults may vomit only once or twice, or merely have nausea, slight abdominal pain and a few loose stools. The diagnosis is established, or rather postulated, from the presence of many cases of vomiting in the community at the same time. Treatment is similar to that discussed in the consideration of cyclic vomiting.

Cyclic or Recurrent Vomiting

Certain children tend to have bouts of vomiting without apparent cause or associated with minor infections. Such attacks occur at irregu-

lar intervals for years, but tend to disappear at puberty. Such children are inclined to be nervous and emotionally unstable, and there is a tendency to migraine in later life. Occasionally such a patient is found to have a peptic ulcer. Premonitory symptoms may be irritability, lethargy, malaise, coated tongue or abdominal pain, or evidence of a minor infection of the upper respiratory tract. Vomiting is frequent and forceful, dehydration occurs, ketosis appears and produces an acetone odor of the breath, and there is often diffuse abdominal pain probably produced by the strain of emesis and retching. Vomiting can usually be controlled adequately by early sedation with barbiturate-containing suppositories, frequent administration of sips of glucose-containing liquids, and subsequent judicious introduction of simple foods low in fat. Parenteral fluid therapy is sometimes required.

Psychogenic Vomiting

Emesis on an emotional basis may occur in the first year of life, but is much more common later on and remains as a frequent cause of vomiting throughout childhood. Recurrent abdominal pain or headache is often an associated symptom. Forcing food, tension at mealtimes, fright, extreme anger or even intense pleasurable anticipation may cause certain children to vomit. Other children vomit from nervous apprehension, such as on examination day or the day of a school play in which they are reluctant actors. Many other causes exist. Unfortunately, many do not think of psychogenic causes and expose the parents to the undue expense and the child to the psychic trauma of an unnecessarily complete battery of tests and procedures.

Allergic Vomiting

Allergy to foods may produce vomiting, milk being the most common offender. Ingestion of the food to which the child is sensitive leads to vomiting, colicky abdominal pain and, frequently, diarrhea. Stools may contain flecks of blood, or larger amounts, and perhaps mucus rich in eosinophils. Other manifestations of allergy may occur, such as eczema or urticaria. Withdrawal of the responsible food from the diet results in dramatic improvement; its reintroduction causes an exacerbation.

Dietary Indiscretions

Dietary indiscretions are well known causes of vomiting. Nowadays, perhaps fewer green apples are eaten, but the juvenile gastric mucosa is frequently confronted with popcorn, peanuts, soft drinks and weird

productions of the soda fountain dripping with syrup and covered with nuts. Bolting inadequately chewed food, or eating while overheated or fatigued, may also cause vomiting.

Reflex Vomiting

Vomiting is a frequent accompaniment of any condition characterized by severe coughing. The fact that pertussis often produces emesis has led to an unfortunate tendency to make this diagnosis in any infant with paroxysmal coughing associated with vomiting. Vomiting may also be the result of a severe postnasal drip, the mucopurulent exudate accumulating in the stomach apparently causing enough gastric irritation to produce vomiting. Pressure of a tongue depressor in visualizing the pharynx causes some children to vomit.

Motion Sickness

Certain children are unusually liable to vomiting when riding in an automobile, on a train or in any moving vehicle, a situation comparable to sea sickness. Some children who have car sickness have a visual difficulty that is accentuated by moving objects and leads to headache and vomiting. The same is true of certain children who cannot watch motion pictures without headache and vomiting. In such instances examination by an ophthalmologist is indicated.

Drugs and Anesthesia

Vomiting may be caused by many drugs, including digitalis, sulfonamides, broad-spectrum antibiotics and even acetylsalicylic acid. Various anesthetic agents may cause vomiting.

Familial Autonomic Dysfunction (Riley-Day Syndrome)

Riley, Day, Greeley and Langford[6] have described an unusual syndrome in which repeated "episodes of cyclic vomiting lasting two or three days and recurring at intervals of weeks or months" occur. All their patients were Jewish, failed to produce tears when crying, exhibited sudden blotchy skin eruption when tense, perspired excessively, had persistent drooling past infancy, were very awkward, had absent or hypoactive deep tendon reflexes after the first year of life, and seemed relatively indifferent to pain. The blood pressure was labile, excitement elicited hypertension, half of the children were mentally deficient, pulmonary infections were common, and corneal ulceration often occurred. No effective treatment has been found.

SUMMARY AND CONCLUSIONS

A discussion of the etiology of vomiting in infancy and childhood has been presented.

Orderly analysis of the case has been stressed, involving chiefly a carefully taken history.

Vomiting in the early neonatal period has been emphasized, chief attention being devoted to conditions that produce obstruction, especially congenital anomalies of the alimentary tract.

The more common causes of vomiting after the newborn period have been discussed.

The hazards of emesis have been stressed, especially the tendency to otitis media and aspiration of vomitus with consequent asphyxia, pneumonia or atelectasis.

Metabolic derangements incident to emesis were mentioned briefly.

Approached in this manner, the study of even so prosaic a symptom as vomiting becomes of great interest, and the patient profits.

REFERENCES

1. Berenberg, W., and Neuhauser, E. G. D.: Cardioesophageal Relaxation (Chalasia). Pediatrics, 5:414, 1950.
2. Gross, R. D.: The Surgery of Infancy and Childhood. Philadelphia, W. B. Saunders Company, 1953.
3. Holt, L. E., Jr., and McIntosh, R.: Pediatrics. 12th ed. New York, Appleton-Century-Crofts, Inc., 1953.
4. Hughes, J. G.: Pediatrics in General Practice. New York, McGraw-Hill Book Company, Inc., 1952.
5. Nelson, W. E.: Textbook of Pediatrics. 6th ed. Philadelphia, W. B. Saunders Company, 1954.
6. Riley, C. M., Day, R. L., Greeley, D. McL., and Langford, W. S.: Central Autonomic Dysfunction with Defective Lacrimation. I. Report of Five Cases. Pediatrics, 3:468, 1949.
7. Riley, C. M., Day, R. L., Greeley, D. McL., and Langford, W. S.: Familial Autonomic Dysfunction. J.A.M.A., 149:1532, 1952.
8. Wilson, H., and Bushart, J. H.: Annular Pancreas Producing Duodenal Obstruction. Ann. Surg., 137:818, 1953.
9. Zuelzer, W. W., and Wilson, J. L.: Functional Intestinal Obstruction on a Congenital Neurogenic Basis in Infancy. Am. J. Dis. Child., 75:40, 1948.

848 Adams Avenue
Memphis, Tennessee

DIARRHEA, VOMITING AND COLIC IN THE YOUNG INFANT DUE TO MILK ALLERGY

JOHN A. BIGLER, M.D.

Though the role of allergy is being more widely accepted as a cause of various disabilities in children, there is still not sufficient awareness of its causative role in the young infant with gastrointestinal symptoms. All too frequently allergy is thought of only in terms of eczema, hay fever and asthma, forgetting that gastrointestinal allergy may manifest itself by some combination of diarrhea, vomiting and colic.

Although gastrointestinal allergy is usually due to foods, it may also be due to other allergens such as inhalants, pollens, molds, drugs, and so forth. Food allergens may also cause symptoms referred to other parts of the body than the gastrointestinal tract. The symptoms of allergy depend upon the shock organ involved. These most commonly are the skin and the mucous membranes of the nose, eyes, bronchi and the gastrointestinal tract. Other organs or tissues may also be involved, but less commonly so. The symptomatology may be that of single or multiple organ or tissue involvement. The shock organ involved seems to have some relation to age. For instance, eczema is more common in infancy than is hay fever or asthma. If one can speak of the progression of allergic manifestations from early infancy, it seems that gastrointestinal allergy occurs earliest, to be followed by eczema, allergic rhinitis and finally asthma. It is commonly accepted that there are four foods—cow's milk, orange juice, wheat and egg white—that most frequently lead to the development of eczema in the young infant. The shock organ producing the symptoms is the skin. The allergen enters the gastrointestinal tract, and so it too may become a shock organ.

The majority of infants receive some cow's milk during early infancy

and increasing amounts thereafter. *The vast majority of infants tolerate cow's milk and never become allergic to it.* But cow's milk allergy is not uncommon, and it is this group that is being discussed. Gastrointestinal allergy to cow's milk may become evident during the neonatal period or shortly thereafter. It takes about seven days to three weeks for allergic symptoms to develop after feeding a cow's milk formula. The symptoms may be solely gastrointestinal, or there may also be transient skin reactions. The severity of the symptoms depends upon the individual infant's sensitivity to the milk protein allergen. Some infants are unable to tolerate even minute amounts of cow's milk, while others can take varying amounts of milk without too much distress. In these latter, increasing the milk intake will often increase the symptoms.

SYMPTOMS

In our experience when gastrointestinal symptoms due to milk allergy occur in the young infant, they are manifested by diarrhea alone in about 35 per cent of the cases, with vomiting and regurgitation alone in 10 per cent and colic alone in 5 per cent. This means that in 85 per cent there is some combination of diarrhea, vomiting and colic as a triad of symptoms. There is usually also an associated failure to gain or slow weight gain. The infant is unhappy and seems anxious to eat frequently. The stools are usually loose to watery and more frequent than normal. They may or may not have a bad odor. They contain more mucus than normal, and at times there is some blood present. The abdomen is likely to be distended and the buttocks excoriated. The symptoms may be constant, or there may be a partial remission for a few days.

The evaluation of the symptoms depends upon the mother's story and the perspective of the examiner. Clein[1] noted the following symptoms in 140 infants allergic to cow's milk:

Vomiting and regurgitation	39%	Mucus in stools	6%
Colic	29%	Blood in stools	5%
Diarrhea	24%	Anorexia and refusal of milk	4%

Rosenblum and Rosenblum[2] studied a similar group of infants and found:

Diarrhea alone	31.6%	Diarrhea, colic and vomiting	20.0%
Vomiting alone	8.3%	Total diarrhea	83.0%
Colic alone	5.0%	Total vomiting	46.6%
Diarrhea and vomiting	15.0%	Total colic	45.0%
Diarrhea and colic	16.0%		

Fever is rarely present except during periods of intercurrent infections and anaphylactic reactions. The symptoms of milk allergy are the same

as those in other diseases of infancy such as parenteral and enteral diarrhea, the celiac syndrome, and so forth.

DIAGNOSIS

The diagnosis of milk allergy in infancy should be comparatively simple if one keeps in mind that it does occur and the triad of symptoms already mentioned. Colic is a poorly defined term used too frequently in infants with gastrointestinal distress. Some physicians still rely on this diagnosis for that group of infants without readily discernible causes for their gastrointestinal symptoms. Many such infants have frequent changes of formula, all of them containing milk.

History. In every history one should note the presence of allergy in the father and mother and in their families as well as in siblings. If there has been allergy in the family, then the physician should be alerted to the possible development of allergy in the infant. Although the allergic state may be transmitted, sensitivity to specific allergens is not.

Symptoms. The usual symptoms of milk allergy when the gastrointestinal tract is the shock organ are some combination of diarrhea or loose stools, vomiting and regurgitation and colic. This is usually associated with a slow weight gain or a failure to gain. At times there may be transient eczematous rashes. Rarely does the sensitivity to milk become so violent as to produce anaphylactic-like periodic symptoms of high fever, joint paint and swelling and extensive urticaria. Occasionally the protein absorption will be so low that nutritional edema will occur.

The gastrointestinal symptoms of milk allergy may be mild or severe. They may last for only a few months or may persist for years. Apparently many infants become desensitized, as happens spontaneously in other forms of allergy.

Physical Examination. The physical findings in patients with cow's milk allergy when gastrointestinal symptoms are present are usually normal or minimal other than abdominal distention and transient allergic rashes.

Laboratory Examinations. All laboratory procedures are confirmatory and not diagnostic in cases of gastrointestinal allergy. The important procedures are simple enough to be done in one's office.

The RED BLOOD CELL COUNT and HEMOGLOBIN are usually normal for the age of the infant except in those cases with anorexia when anemia may be present.

In the DIFFERENTIAL COUNT of the peripheral blood there may be a slight increase of eosinophils of 4 to 15 per cent. Even in severe or protracted cases the eosinophile count may be normal.

STOOL EOSINOPHILE COUNT. The normal stool contains only a few or

no eosinophils. When there are gastrointestinal symptoms of milk allergy, there is a marked increase in eosinophils of 15 to 100 per cent. We have rarely had a case with less than 25 per cent. At times when a child is recovering from an enteral or parenteral diarrhea, we have seen eosinophile counts up to 20 or 25 per cent. This disappears upon recovery, when the stools become normal.

Stool eosinophile counts are simple to do and may be an office procedure. A smear of the mucus from a freshly passed stool (not of the stool itself) is made and stained with Wright's stain. The eosinophils per 100 cells are counted.

SKIN TESTS WITH COW'S MILK CASEIN AND WHEY. It is generally believed that skin tests in infants are of limited value. They at least can be of confirmatory value. We have found the intradermal skin test positive in most infants with proved cow's milk allergy.

In the young infants we have not felt that ROENTGENOGRAPHIC STUDIES of the gastrointestinal tract with or without barium have been of any help. Proctoscopic examination has been of no help in making a diagnosis. A good therapeutic test for diagnosis is to eliminate milk from the diet for a few days or until the symptoms subside and then reintroduce a milk formula and watch for recurrence of symptoms.

TREATMENT

The main treatment of gastrointestinal allergy due to cow's milk is the elimination of cow's milk from the diet. There are several good milk substitutes on the market that supply all the calories, carbohydrates, fats, proteins, minerals and vitamins that are needed for adequate infant nutrition.

The easily available milk substitutes are goat's milk (fresh or evaporated), soy bean milks such as Mulsoy, Sobee and Soylac, Nutramigen and meat base formula. They should be used in the recommended dilutions. We have found that with the soy bean milks it is advisable to start with weaker than normal dilutions at first because they may produce loose stools. Goat's milk is less likely to give complete and permanent relief of symptoms because it contains the same type of casein as does cow's milk. Also, occasionally with the soy bean preparations, the allergic infant may become sensitized to soy bean protein with the recurrence of symptoms or the development of eczema. It is our custom to sweeten most of these preparations with some saccharin so that they will be taken better.

We have not found the antihistamine preparations of any value except possibly for their mild sedative action.

With the milk substitutes there is usually a dramatic relief of symptoms within a few hours to several days.

Some physicians feel that the infant should be allowed some cow's milk so that he will desensitize himself. We feel that this is of no value. We completely eliminate the cow's milk and find that most infants can again take it after a period of several months, while in others it may be longer. Small amounts of milk can be tried after three or four months and, if tolerated, can be increased until the infant is completely back on milk again.

We have not encountered gastrointestinal allergy to the common carbohydrates used in supplementing infant formulas.

CASE REPORTS

A few representative case reports of milk allergy in infants are presented.

Diarrhea and Colic

CASE I. C.R. was born after a normal pregnancy and delivery. He was first seen at the age of 20 days with a history of diarrhea, 15 to 20 stools a day, since the age of 10 days. There was no vomiting, but irritability, incessant crying and abdominal distention. Cow's milk, evaporated milk and protein milk formulas had been tried. Feedings were 3 ounces every 3 hours. The birth weight had been 6 pounds and 8 ounces, and the present weight was 6 pounds and 5 ounces.

Both parents were allergic, as were 2 siblings, ages 3 and 5. Only the mother had a cow's milk allergy.

Physical examination was normal except for poor nutrition, slight dehydration, irritability, a distended abdomen and redness of the buttocks. The blood cell count was normal, and there was only 1 per cent eosinophils in the differential count of the white cells. There were 75 to 80 per cent eosinophils in the stool mucus.

The infant was placed on a Mulsoy formula with immediate improvement. The diarrhea stopped at once, as did the distention of the abdomen, the irritability and the crying. In 7 days the baby gained from 6 pounds and 5 ounces to 7 pounds and 1 ounce. Because of the allergic family history this baby has been kept on soy bean milk voluntarily by the mother for the past 3 years. There has been no recurrence of gastrointestinal symptoms.

Diarrhea, Colic, Hypoproteinemia and Anemia

CASE II. M.S. was born at term after an uncomplicated pregnancy and delivery. The birth weight was 7½ pounds.

The infant was entirely breast fed for the first 3 weeks of life and did well. Because the weight gain did not seem satisfactory, nursing was discontinued and a fresh cow's milk formula with added carbohydrate was substituted. About one week later the infant began to have 10 to 12 watery, green, foul-smelling stools with mucus daily. During the next 2 months he had many formula changes—protein milk, evaporated milk and condensed milk with or without barley water. He had also received antibiotics. At this time when he was seen by us he was having some red blood in his stools. He was pale and irritable and passed a good deal of flatus.

On examination the infant was an alert, pale infant with moderate, generalized edema. There was some scaly dry red rash on the cheeks and forehead. The nasal mucous membranes were pale. The liver and spleen were palpable one fingerbreadth below the costal margin.

There was a positive family history of allergy. The mother has seasonal hay fever and asthma, and of 3 siblings one is allergic to liver and eggs.

The red blood cell count was 3,100,000; the hemoglobin, 6.1 gm.; and the white cell count, 18,900, with 12 per cent eosinophils in the differential count. The total eosinophile count was 943.7 per cubic milliliter, and the reticulocyte count was 4.2 per cent. The fasting nonprotein nitrogen was 49 mg. per 100 ml., the total proteins 2.3 gm., with an alpha-globulin ratio of 1.6/0.7. The serum cholesterol was 103 mg. per 100 ml. Only a few fat granules were seen on examination of the stool. Stool cultures and smears were negative for pathogenic organisms, ova and parasites. Several stools were examined for eosinophils, and 35 to 60 per cent were present each time.

Skin scratch tests were negative for cow's milk whey and casein. Intradermal tests were 3 + positive for cow's milk whey and 2 + for casein.

The diagnosis was gastrointestinal allergy to cow's milk, hypoproteinemia with edema and nutritional anemia.

The baby was given blood transfusions and placed on a 1:3 Mulsoy formula. There was an immediate change in personality, the diarrhea subsided, and the rash disappeared, as did the diarrhea and edema. The admission weight was 13½ pounds. This dropped in a few days to 11½ pounds, after which a steady gain occurred. After several days the formula was increased to a 1:2 mixture of Mulsoy.

The baby has since remained well.

Vomiting

CASE III. S.J. was first seen at 3 months of age. She was a colored female born by cesarean section after 7½ months' gestation. The birth weight was 4 pounds and 3½ ounces, and she was not released from the hospital until one month of age. The mother knew nothing about this period. She was discharged on a 1:2 evaporated milk formula with no added carbohydrate. This same formula had been continued. Since being home she had vomited, sometimes projectilely, 15 to 20 minutes after every feeding.

Three weeks prior to admission here she had a severe diarrhea for which she was admitted and remained in another hospital for 2 weeks, being treated with intravenous fluids. At that time her weight was 6¾ pounds. She continued to vomit every feeding and had diarrheal stools.

There was no history of allergy in the parents. One sibling had vomited until 3 months of age.

On examination she was a thin, dehydrated, tense female with a distended abdomen and bilateral inguinal hernias. The urine was normal; the red blood cell count was 3,880,000; the hemoglobin, 11.4 gm.; the white blood cell count, 11,450, with a normal differential count. The nonprotein nitrogen was 47 mg. per 100 ml.; the total proteins, 5.9 gm., with a normal alpha-globulin ratio. The carbon dioxide was 18.0 milliequivalents per liter, the sodium 130.64 milliequivalents per liter, the potassium 4.10 milliequivalents per liter, the chlorides 108 milliequivalents per liter, and the *p*H 7.52.

The infant was taken off everything by mouth and given intravenous fluids. The vomiting and diarrhea subsided. Darrow's solution given by mouth was retained, but when skimmed milk was started, there was recurrence of the vomiting. Phenobarbital, atropine and changes of formulas did not help. An intravenous pyelogram was normal, as were fluoroscopic examinations of the gastrointestinal tract with barium.

At this time there were 100 per cent eosinophils in the stool mucous smears.

She was placed on a 1:3 and then 1:2 Mulsoy formula. The gastrointestinal symptoms subsided immediately, and she began to act like a normal baby. In 4 weeks she gained from 5½ to 8 pounds. The stool eosinophils decreased to 5 per cent. The intradermal skin test was strongly positive for cow's milk casein.

During the next 3 months her weight became normal for her age. She has remained well on a soy bean formula.

Diarrhea, Colic, Fever and Eczema

CASE IV. H. was first seen at the age of 3 months. He had not been breast fed, but was started on a 1:2 evaporated milk formula. When about 2 weeks of age, he began to cry excessively, and the mother thought he was hungry. She began on her own initiative to increase his formula so that he was finally taking 2 cans of evaporated milk diluted with 13 ounces of water. His crying and distress continued. He was having an increasing number of stools, marked abdominal distention, an increasing amount of eczematoid rash and, for the past few days, some fever.

On examination the temperature was 105° F.; there was a generalized eczematoid rash over the whole body that can best be described as giving him the appearance of a "boiled lobster." There was marked abdominal distention, and the baby was thoroughly unhappy. No findings of infection were present.

There was no history of allergy in the parents or in the only other sibling.

Because of the large amount of cow's milk this baby was receiving, the colic, frequent stools and the rash, it was thought this might be a milk allergy, and without laboratory investigation the infant's formula was changed to evaporated goat's milk. Within 24 hours there began a rapid change for the better, and within a week all symptoms had completely disappeared. He was satisfied with 13 ounces of evaporated goat's milk diluted with 18 ounces of water and 2 nonwheat cereal feedings daily.

Within 6 months this infant was back on a regular evaporated milk formula and has tolerated normal amounts of cow's milk since that time.

In this infant there was only presumptive evidence of cow's milk allergy without any laboratory confirmation. It is possible that the infant would have tolerated a normal amount of cow's milk protein, but the zeal of the mother in interpreting hunger for colic pushed the baby beyond its tolerance. The complete relief of symptoms of allergy would seem to make this a case of cow's milk allergy rather than one of simple overfeeding.

Cases V and VI are illustrative of older children with gastrointestinal cow's milk allergy present since infancy, but not recognized.

CASE V. A.M. was first seen when he was 7 years of age because of slow gain, vomiting and headaches.

The pregnancy and birth history were normal. The birth weight was 7 pounds and 10 ounces. He was started on breast feedings, but was changed to a cow's milk formula before he left the hospital because he did not gain.

During infancy and up to 2 years of age he vomited after every feeding, had several loose stools a day, occasionally with blood in them, severe colic, failure to gain and was extremely unhappy. Because of this feeding problem he was not started on orange juice and vitamins until one year of age. There were many changes of formula all of which contained cow's milk. After 2 years of age he became constipated, would eat only bread and butter and jelly, and would take only 6 to 8 ounces of milk a day. He continued to vomit frequently.

During the past 2 years, besides the foregoing symptoms, he has had severe headaches, severe abdominal pain, pain in his knees, nausea and vomiting. These occurred especially during the night about 5 times a week. It was then brought out in the history that these symptoms began when the child started nursery school, at which time he was forced to take one or more glasses of milk between meals. This doubled to tripled his usual milk consumption.

The only pertinent fact in the family history was "miner's asthma" in the father. One 2 year old sibling was normal.

The developmental history was normal. He had had the usual immunizations,

chickenpox and measles, and hay fever in the fall for which he received hay fever capsules. The mother had noticed that he could not tolerate eggs and chocolate.

He had been taken care of by 3 different physicians with the following diagnoses: (1) nervous stomach, (2) pylorospasm, (3) spastic colon, (4) behavior problem, (5) allergic rhinitis, (6) undernutrition, (7) dental caries, and (8) scurvy. Many laboratory procedures had been done, such as complete gastrointestinal examination with barium. All had been negative. Many therapeutic measures had been advised, such as changes in food, tonics and vitamins, sedatives, glasses, allergy capsules and psychotherapy for the mother.

On physical examination he was a thin, active child with good color, appearing younger and smaller than his chronologic age. The only other abnormal finding was severe dental caries and a left undescended testicle. His weight was only 37½ pounds.

The blood cell count was normal, and no eosinophils were present in the differential smear. The urine was negative. Stool examination was negative for bacteria, ova and parasites. The fat content was normal. The chemical test for blood was 4 plus. No stool eosinophile count was done on the stool because no mucus was present. Roentgenograms of the skull, chest and of the wrists were normal. The glucose tolerance test was as follows: fasting, 97; one-half hour, 142; one hour, 153; two hours, 107; and three hours, 70. The Mantoux and histoplasmin skin tests were negative.

Intradermal skin tests for cow's milk casein, egg white, banana and house dust were all 4 +.

The only therapeutic measures were elimination of cow's milk and egg from his diet. His vomiting, abdominal pain and headaches immediately disappeared, and his appetite and disposition improved. It would seem that this boy's primary difficulty was a cow's milk allergy with the secondary development of egg, banana and house dust allergy.

Case VI. S.B. was first seen at the age of 7 years with a history of high fever, rash and swollen joints occurring over the past 2 years at fairly regular intervals of every 3 to 4 weeks. She was observed during one of these typical episodes. The fever suddenly rose to 104° F.; there was swelling and pain of the hands and feet, wrists and ankles, knees and elbows, and a diffuse blotchy urticarial rash with dermographia and anorexia. The joints were hot, tender and painful on motion. There was no evidence or findings of an infection. The whole episode in spite of any therapy would last for about 4 days, when all the symptoms and findings would subside except for occasional hivelike lesions which would always be present.

As an infant she had always been on a cow's milk formula. There had been slow weight gain and colic. She was always a feeding problem. The birth weight was 6½ pounds.

The family history of parents and 4 siblings was normal.

Physical examination was completely normal except for underweight and some scattered urticarial wheals.

The blood cell count was normal with only 1 per cent eosinophils in the differential count. Unfortunately, a stool eosinophile count was not done.

Because the symptoms were like those of an anaphylactoid serum reaction, allergy was suspected. That the allergen was cow's milk seemed possible because of the gastrointestinal symptoms during infancy. Also a food taken daily as is milk would be a more plausible cause than a food taken regularly at 3 to 4 week intervals just before the onset of symptoms.

Intradermal skin tests were positive only for cow's milk casein.

With elimination of cow's milk from the diet, there has been no recurrence of any of the symptoms during a 10 year follow-up. The weight has increased to normal.

CONCLUSIONS

1. Cow's milk allergy in the young infant is not uncommon.
2. Gastrointestinal allergy should be suspected in young infants with some combination of diarrhea, vomiting and colic.

3. The laboratory tests confirming cow's milk gastrointestinal allergy are simple and can easily be an office procedure.

4. The young infant's skin does react satisfactorily to allergens, and these tests can be used as confirmation to the clinical symptoms.

5. Treatment is simple—the elimination of cow's milk and the substitution of a nonmilk formula.

REFERENCES

1. Clein, N. W.: Cow's Milk Allergy in Infants. Ann. Allergy, 9:195, 1951.
2. Rosenblum, A. H., and Rosenblum, P.: Gastro-intestinal Allergy in Infancy, Significance of Eosinophils in Stools. Pediatrics, 9:311, 1952.

707 Fullerton Avenue
Chicago 14, Illinois

BLOOD IN THE STOOLS OF INFANTS AND CHILDREN

THOMAS G. BAFFES, M.D.

WILLIS J. POTTS, M.D.

Blood in the stools of infants and children is an alarming symptom, and accurate diagnosis is essential for correct treatment. The clinician's ingenuity is sometimes severely taxed before the etiology is discovered. Nevertheless, proper therapy brings gratifying relief or may even be lifesaving. It is a curious fact that the type and severity of rectal bleeding may be useful in differential diagnosis. Severe rectal bleeding frequently indicates a surgical lesion. Milder

TABLE 18. *Rectal Bleeding Symptoms*

	CASES	PER CENT
Severe bloody diarrhea	99	43.4
Diarrhea with occasional bloody stool	51	22.3
Neonatal rectal bleeding of undetermined origin	27	11.9
Bleeding from visible anal or rectal lesions	40	17.6
Tarry stools	11	4.8
	228	100.0

rectal bleeding is usually associated with lesions that can be treated conservatively. The presence or absence of diarrhea is also of diagnostic value, while tarry stools frequently indicate systemic diseases requiring complicated and prolonged management.

In order to help evolve a system of differential diagnosis of rectal bleeding in childhood, we reviewed all such cases admitted to the Children's Memorial Hospital from January, 1948, through December, 1953. Two hundred and twenty-eight patients were studied. In general, five distinct clinical syndromes were noted (Table 18), each caused by a

From the Department of Surgery, Children's Memorial Hospital, Chicago.

number of specific clinical entities. Although each group had the atypical case which deviated from the generalities implied in this classification, there was fairly close correlation between the syndromes and their respective component clinical entities. It was possible to predict with reasonable accuracy the type of lesions present, when a particular clinical syndrome was encountered. The syndromes and their component entities will be described in detail.

SEVERE BLOODY DIARRHEA

Ninety-nine patients, or 43.4 per cent of the series, passed copious amounts of fresh blood per rectum. Generally, the stools were loose and consisted almost entirely of bright red or "currant-jelly" blood. Associated systemic symptoms were rare, except for evidence of shock. This

TABLE 19. *Clinical Entities Included in Each Rectal Bleeding Syndrome*

	CASES	PER CENT
1. Severe blood diarrhea:		
Meckel's diverticulum	23	10.1
Intussusception	60	26.3
Polyps	16	7.0
Total	99	43.4
2. Diarrhea with occasional bloody stool:		
Enterocolitis	34	14.9
Ulcerative colitis	6	2.6
Proctitis	11	4.8
Total	51	22.3
3. Neonatal rectal bleeding of undetermined origin	27	11.9
4. Bleeding from visible anal or rectal lesions:		
Anal fissure	25	11.0
Fistula in ano	5	2.2
"Hemorrhoids"	2	0.9
Rectal prolapse	7	3.1
Anal laceration (in hemophiliac)	1	0.4
Total	40	17.6
5. Tarry stools:		
Duodenal ulcer	3	1.32
Biliary atresia	1	0.44
Cirrhosis of liver	1	0.44
Thrombocytopenic purpura	2	0.88
Banti's syndrome	3	1.32
Hemorrhagic disease of newborn	1	0.44
Total	11	4.84

group contained 23 patients with Meckel's diverticulum, 60 patients with intussusception and 16 patients with rectal or colon polyps (Table 19).

Meckel's Diverticulum

The most severe rectal bleeding in infants and children was usually associated with symptomatic Meckel's diverticulum. There were no prodromal symptoms and no significant associated abdominal findings. The patient usually had a history of sudden onset of silent, copious rectal bleeding, frequently of alarming proportions. Large quantities of

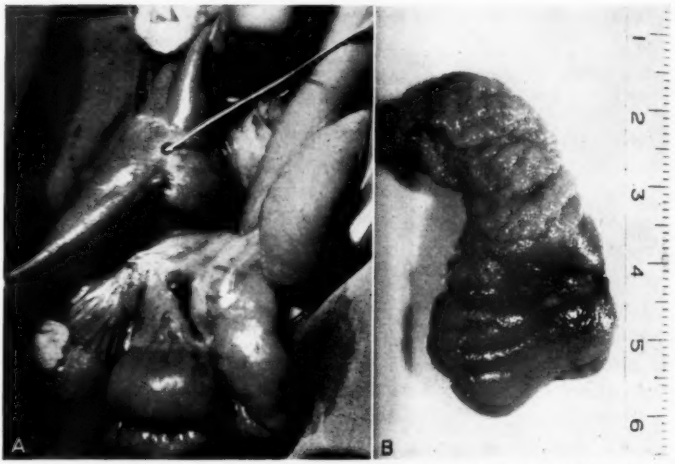


Fig. 16. *A*, Meckel's diverticulum which had caused episodes of rectal bleeding and had finally developed perforation of the peptic ulcer located at its base. *B*, Surgical specimen of a Meckel's diverticulum opened to show the peptic ulcer at its base. Microscopic examination revealed gastric epithelium in the mucosal lining of the diverticulum.

dark red clotted blood were passed. Apprehension, thready tachycardia, cold, clammy skin and other signs of shock were sometimes noted. The episodes were single or recurrent. The duration of symptoms prior to admission to the hospital varied from less than 24 hours to over one year. The age of the patients ranged between three months and 12 years.

It is interesting that, of 27 symptomatic Meckel's diverticula treated in our Hospital during this six year period, 23 patients, or 85 per cent, were admitted with severe rectal bleeding. In the vast majority of these cases ectopic gastric mucosa was present in the diverticulum, and bleeding was secondary to peptic ulceration in the base of the diverticulum or in the wall of the adjacent small bowel (Fig. 16).[2] Attempts were

made to treat the patient conservatively with multiple transfusions. After bleeding had ceased the patient was prepared for operation, and the diverticulum was removed. If the bleeding did not cease, emergency laparotomy was done.

CASE I. C.K., a 6 months old boy, was admitted to the Hospital on July 29, 1949, with a history of passing copious, dark red bloody stools on July 19 and 27. He had been hospitalized elsewhere immediately after the second episode of rectal bleeding and had received multiple transfusions. The bleeding had stopped, and he was transferred for exploratory laparotomy. Preoperative blood studies indicated a hemoglobin of 11.6 gm. and a red blood cell count of 4,040,000. Operation was performed on August 1, and the Meckel's diverticulum was excised, the stump being oversewn obliquely and inverted into the small bowel lumen. He had an uneventful postoperative course and was discharged on August 5. Gross and microscopic examination of the surgical specimen revealed a peptic ulcer in the base of the Meckel's diverticulum. In the diverticulum, near the ulcer, typical gastric mucosa was found.

Intussusception

Patients with intussusception also had bloody stools as an integral part of their clinical syndrome, although the rectal bleeding was less severe and more variable. Characteristically, an apparently healthy male child was admitted with a history of sudden onset of severe recurrent and recrudescent abdominal colic associated with vomiting. A doughy abdominal mass was usually palpable in either the upper or lower left abdominal quadrant, depending upon the extent of intussusception. There was no evidence of peritonitis. Digital examination frequently disclosed a palpable cervix-like mass in the rectum. A "currant-jelly" stool or bright red blood usually appeared immediately after the onset of symptoms, although it occasionally was delayed. Bleeding was moderate, but sometimes was so severe that the patient showed signs of shock. In most cases the history of repeated severe abdominal colic, a palpable abdominal mass and characteristic "currant-jelly" stools made the diagnosis so definite that a confirmatory barium enema was not necessary.

CASE II. D.R., a 10 months old white boy, was admitted to the Hospital on May 12, 1953, with a history of vomiting for 2 days before admission. On the morning of admission he had passed a copious loose stool consisting of dark red clotted blood. He had cried all night, but the parents had not observed any evidence of severe abdominal cramps. The past history was noncontributory except for a 3 day bout of diarrhea that had occurred one week before admission and had responded to Terramycin. On physical examination there were no abdominal masses. Rectal examination revealed only dark red blood on the examining finger.

A barium enema was done, and the diagnosis of intussusception was established (Fig. 17). During the barium enema the intussusception was reduced. The terminal ileum, however, was not satisfactorily visualized, and reduction could not be considered definitely completed. It was decided to observe the child for a few hours, utilizing the time for hydration.

Within 4 hours after termination of the barium enema the child began to cry out with pain, at intervals of about 10 to 15 minutes. A mass became palpable in the left upper quadrant of the abdomen, and the peristalsis became high-pitched. A laparotomy

was performed through a McBurney incision in the right lower abdominal quadrant. A recurrent ileo-ileal intussusception was found extending into the transverse colon. This was reduced manually, and no bowel resection had to be done. The patient had an uneventful postoperative course and was discharged on May 19. The symptoms have not recurred.

In patients with intussusception, seen within a few hours after the onset of symptoms, barium enema reduction may be attempted by a radiologist skilled in this technique. Such reduction is fraught with uncertainty, however, and failures are frequent when it is attempted after prolonged duration of symptoms. Unless the barium enema adequately

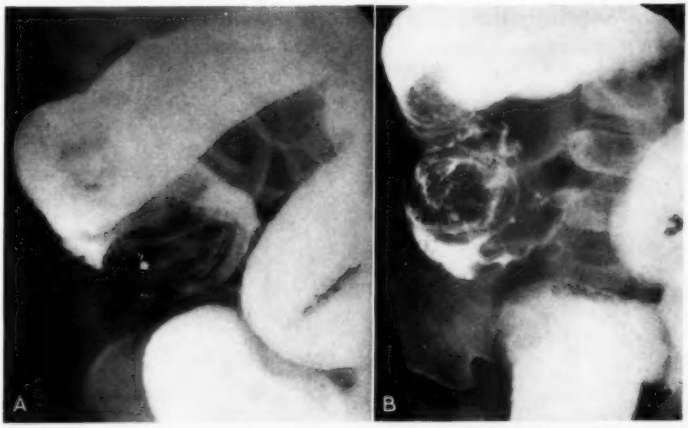


Fig. 17. *A*, "Spot" roentgenogram demonstrating the use of barium enema to establish the diagnosis of intussusception. Note the "chalice sign" in the cecal region, caused by protrusion of the intussusception into the lumen of the bowel. *B*, In spite of sustained pressure with the barium, the terminal ileum failed to visualize satisfactorily.

demonstrates the terminal ileum and the symptoms subside completely, one is obligated to explore the child's abdomen. Generally, exploratory laparotomy with gentle manual reduction of the intussusception was the treatment of choice in our hands. In most cases no cause for the intussusception was found at operation. Of 60 cases in this series, only three were associated with a Meckel's diverticulum, and one had multiple polyps of the small intestine. The latter case had recurrent small bowel intussusception and has been reported previously.[4] It was of considerable interest because it illustrated the pigmentation of the lips and buccal mucosa which is thought to be characteristically associated with multiple polyps of the small intestine (Fig. 18).[1, 3]

Polyps

Polyps in the large bowel had variable symptoms, depending upon their location in the colon or rectum: (1) Patients with polyps located

high in the colon usually were admitted with the presenting complaints of pallor, weakness, listlessness or easy fatigability. Examination of the peripheral blood revealed anemia, with a low red blood cell count and low hemoglobin. Rectal bleeding usually was occult and therefore was not noted by the parents. One such patient occurred in this series. (2) The remaining patients had polyps located low in the colon or in the rectum. Bleeding was usually dramatic and severe and often accompanied or immediately followed defecation. The parents typically stated that, after a bowel movement, the patient continued to strain or asked to return to stool. A variable amount of bright red blood was then passed. Frequently the polyp protruded beyond the anus and was seen by the parents.

Fig. 18. Pigmentation of the lips associated with multiple polyposis of the small intestine.

Polyps low in the colon or rectum were usually accessible for diagnosis and removal through the proctoscope. Polyps too high in the colon to be seen through the proctoscope required barium enema for diagnosis (Fig. 19). Their treatment involved laparotomy and colotomy. One patient had multiple polyposis of the large bowel and required total colectomy and ileoproctostomy, after multiple fulguration of the polyps in the lower rectum.

Case III. D.A., a 6 year old boy, was admitted to the Hospital on September 17, 1950, with a history of intermittent diarrhea and bright red bloody stools for 2 years before admission. At the height of his diarrhea he had had as many as 10 to 15 bloody stools daily. Physical examination on admission to the Hospital revealed only an anemic, undernourished boy who did not appear acutely ill. Proctoscopic examination revealed multiple polyps which, on barium enema, were found to extend into the transverse and ascending colons (Fig. 20). A diagnosis of multiple polyposis was made.

The patient was admitted 4 times to the Hospital between October, 1950, and January, 1951. Repeated proctoscopic excision and fulguration of rectal polyps was done until the lower rectum was free of polyps. He was then readmitted on February 8, 1951, and a total colectomy with ileoproctostomy was performed. Microscopic examination of the surgical specimen failed to reveal any evidence of malignancy. He had

a satisfactory postoperative course and was discharged on March 4. He did well until August, 1951, when he had 2 attacks of abdominal pain and vomiting that were suggestive of intestinal obstruction, but responded well to conservative treatment. On August 29, 1951, and again on January 2, 1952, he was admitted to the Hospital for recurrent intestinal obstruction. On each occasion he had exploratory laparotomy with lysis of adhesions. Both postoperative courses in the Hospital were uneventful. He has been asymptomatic and has done well since January, 1952.

DIARRHEA WITH OCCASIONAL BLOODY STOOLS

Fifty-one patients, or 22.3 per cent of the series, had symptoms consisting predominantly of diarrhea. This group contained 34 patients

Fig. 19. Barium enema of a patient with a large solitary polyp in the sigmoid colon. The filling defect confirmed the clinical diagnosis.

with enterocolitis, six patients with ulcerative colitis and 11 with proctitis (Table 19). The characteristic symptom in all these patients was diarrhea—loose, watery stools associated with mucus or pus. Only small streaks of blood occasionally were found mixed with the stools. In rare cases of extremely toxic diarrhea or prolonged ulcerative colitis, moderately severe rectal bleeding occurred. All patients in this group responded to conservative management with the exception of one with ulcerative colitis who came to surgery after prolonged and repeated supportive measures had failed. It is interesting to note that the 34 cases of enterocolitis included approximately 10 per cent of all the patients with infantile diarrhea admitted to the Hospital during the period of study.

CASE IV. B.S., a 2 weeks old girl, was admitted to the Hospital on April 24, 1952, with a history of diarrhea since 6 days after birth. She had passed 6 to 7 loose watery stools daily for about 10 days prior to admission to the Hospital. For 5 days before admission there had been an occasional bloody tinge to the watery stools. No massive rectal bleeding had occurred, and no vomiting was noted. The patient had been taking her formula well. On admission oral alimentation was temporarily withdrawn, and intravenous fluids were given. The next day boiled skim milk formula was offered and was retained. Sulfasuxidine was given by mouth. The diarrhea subsided, and the patient was discharged on May 12. Cultures and microscopic examination of the stools failed to reveal any specific cause for the diarrhea.

CASE V. M.M., a 12 year old girl, was first admitted to the Hospital on November 4, 1947, with a history of diarrhea and occasional bloody stools for 4 years before admission. At the height of her attacks she had passed 9 to 15 stools per day. Rectal bleeding

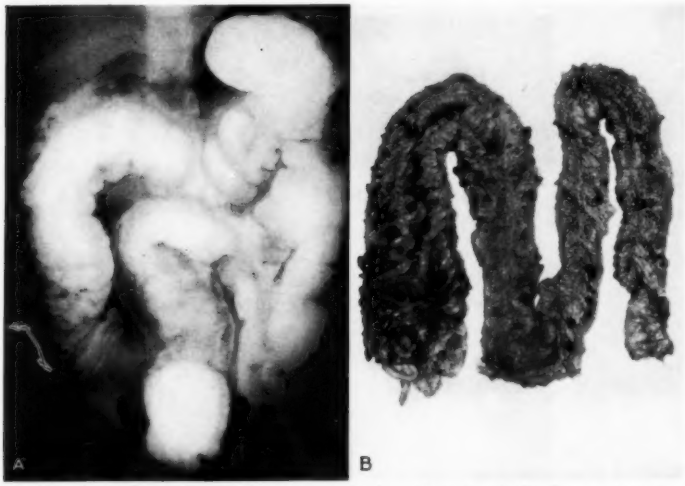


Fig. 20. A, Barium enema showing multiple polyposis of the large intestine. *B*, Surgical specimen after colectomy. Most of the polyps in this particular patient were in the cecum and ascending colon.

had been most severe just after the onset of her symptoms and had decreased for the last 2 years before admission to the Hospital. Since the bleeding had decreased, increased amounts of mucus and pus had been noted in the stools. She had had recurrent fever and abdominal cramps with chronic weight loss. She was brought to the Hospital in November, 1947, because diarrhea with fever and abdominal distention had developed. On admission, moderately severe anemia was noted, and multiple blood transfusions were given. Proctoscopic examination and barium enema confirmed the diagnosis of chronic ulcerative colitis (Fig. 21). Stool cultures failed to demonstrate a specific etiologic agent. On November 11 an ileostomy was done in the right lower abdominal quadrant. She had a satisfacttory postoperative course, and her acute symptoms subsided. She was discharged on November 17, 1947.

After discharge from the Hospital, she improved rapidly, gaining over 25 pounds during the succeeding 9 months. However, early in 1949 she became listless, began to lose weight again and had marked increase in the amount of pus draining from the rectum. She was readmitted to the Hospital on March 9, 1949. After adequate preoperative preparation a colectomy was performed on March 14, 1949. Her postoperative course was good, and she improved considerably. She did well thereafter until March

20, 1950, when she had intestinal obstruction due to postoperative adhesions. On March 22, 1950, she had exploratory laparotomy with lysis of adhesions and revision of her ileostomy. Except for a bout of pyelitis in May, 1950, she did well postoperatively through 1952, when she became over age and stopped coming for follow-up visits. We learned, about a year later, that she had died at home of a sudden, undiagnosed febrile episode.

NEONATAL RECTAL BLEEDING OF UNDETERMINED ORIGIN

In the neonatal period a number of infants have a single bout of bright red blood per rectum, without any other abdominal or rectal findings. This alarms parents and clinician, but, although a number of

Fig. 21. Barium enema demonstrating disappearance of colonic haustrations characteristic of chronic ulcerative colitis.

newborns with this syndrome have been subjected to extensive diagnostic studies, no cause for the rectal bleeding can be found. The symptoms subside spontaneously and usually do not recur. Twenty-seven patients, or 11.1 per cent of the series, were in this category.

Theories concerning the possible etiology of such neonatal rectal bleeding vary from undetected anal fissures to subclinical hypoprothrombinemia. However, laboratory studies, proctoscopic examination, barium enema and gastrointestinal series consistently fail to provide any definite etiology. The important thing to remember about this group is that they respond to expectant care supplemented with vitamin K therapy. It seems wise to forego extensive diagnostic manipulations in fragile newborn infants with such rectal bleeding, unless they have repeated bleeding or manifest other indications for further study.

CASE VI. R.M., a 2½ months old boy, was admitted to the Hospital on January 8, 1950, with a history that 5 days after birth he had had rectal bleeding during and immediately after a bowel movement. Bleeding consisted of bright red blood covering the stool and was associated with screams of pain during defecation. The symptoms recurred several times thereafter at intervals of 3 to 5 days. They then ceased spontaneously under vitamin K and mineral oil therapy. Although a careful examination was done, no definite anal fissure was noted.

About 3 days before admission to the Hospital in January, 1950, the patient had an episode of vomiting and passed a tarry stool. The parents and physician became alarmed, and the patient was admitted for evaluation. Physical examination on admission was entirely negative. Proctoscopic examination and barium enema failed to reveal any lesion of the colon, rectum or anus. Gastrointestinal series was not remarkable. The platelet count was normal, and there was no evidence of anemia or leukocytosis. A diagnostic exploratory laparotomy was considered, but was postponed. The patient was discharged, and no bleeding has recurred since that time. If bleeding does recur, laparotomy will be done with a presumptive diagnosis of Meckel's diverticulum.

BLEEDING FROM VISIBLE ANAL OR RECTAL LESIONS

Forty patients, or 17.6 per cent of the series, had mild to moderate rectal bleeding associated with lesions of the anus or rectum that were detectable by physical examination. The associated lesions frequently responded to conservative measures, including low residue diet and mineral oil.

Twenty-five patients had acute *anal fissures* and usually presented a characteristic clinical syndrome: Almost invariably the child was an infant. The parents usually stated that the patient screamed in pain during defecation. Occasionally, bright red blood was noted covering the stool. Physical examination revealed a small anal fissure which disappeared under administration of mineral oil to maintain soft stools. No operation was required.

Patients with *fistula in ano* sometimes responded to injection of hydrogen peroxide into the fistulous tract. Usually this failed to eradicate the fistula, and fistulectomy was done in the usual manner. Two patients had hemorrhoidectomy, and microscopic examination of the surgical specimens revealed dilated venous sinuses. These may well have been hemangiomas, because hemorrhoids in infants and children are extremely rare. In most cases of rectal bleeding associated with hemorrhoid-like anal tags, it is more likely that the bleeding is due to an acute anal fissure which will respond to mineral oil and a bland, low residue diet.

The treatment of *rectal prolapse* is extremely interesting and could easily be the subject of a separate communication. Although a number of patients with rectal prolapse have been seen, only seven had rectal bleeding and were included in this series. Two of these seven responded well to manual reduction of the prolapsed rectum, administration of mineral oil by mouth, a low residue diet, and strapping the buttocks together with tape. Three others were treated by rectal Sylnasol injec-

tion, combined, in two of them, with Bryant's overhead traction for about ten days (Fig. 22). The Sylnasol induced perirectal fibrosis, and the rectal prolapse did not recur. In the remaining two patients these conservative measures failed, or the prolapse was so severe or of long standing that they were not feasible. Excision of the prolapsed rectum, as it protruded through the anus, was done, with end-to-end anastomosis of the rectal stumps. Both patients had associated exstrophy of the bladder.

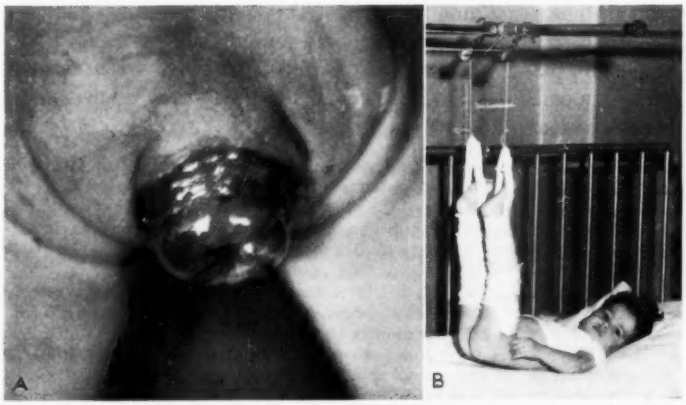


Fig. 22. A, Patient with a rectal prolapse that failed to respond to manual reduction and strapping of buttocks. Perirectal Sylnasol injection was performed, and the prolapse did not recur. *B*, After perirectal Sylnasol injection, Bryant's traction may be utilized until perirectal fibrosis is complete.

CASE VII. S.B., a 2½ year old girl, was admitted to the Hospital on July 25, 1949, with a history of recurrent rectal prolapse for 5 months before admission. She had had no improvement on a low residue diet, mineral oil, and strapping of her buttocks with tape. It was decided to perform perirectal injection of Sylnasol in an attempt to produce perirectal fibrosis. On July 29 the patient was anesthetized, and, with the left index finger in the rectum, multiple injections of Sylnasol were made submucosally, about one inch above the anal verge, placing approximately 0.1 cc. in each site of injection. The buttocks were strapped together with tape, and the patient was sent home to continue the previous conservative regimen. Bryant's traction was not considered necessary because the prolapse was mild, the parents were alert and intelligent, and the child was quite cooperative. The postoperative result was satisfactory; the rectal prolapse has not recurred.

TARRY STOOLS

There were only 11 patients with definite tarry stools, but it is apparent that this group could have been expanded more or less indefinitely if patients with occult blood in the stool were included. Generally, the clinical entities producing tarry stools were systemic and produced

bleeding high in the gastrointestinal tract. Frequently they were associated with oral hemorrhage. The source of bleeding was often diffuse and was not amenable to direct surgical correction. Treatment usually had to be indirect and involved prolonged and complicated medical and surgical care. Of the 11 patients in this group, only one required immediate, direct surgical intervention. This was a patient with severe exsanguinating hemorrhage from a duodenal ulcer. The bleeding did not stop under conservative management, and laparotomy was performed. A bleeding vessel in the base of the ulcer was ligated, and he recovered. The remaining patients, if they had operation, had surgery aimed at correcting the underlying systemic disease that had produced the bleeding—e.g., exploration for biliary atresia, splenectomy for thrombocytopenic purpura, portacaval or splenorenal shunt for portal hypertension, and the like.

CASE VIII. R.P., a 9 year old boy, was admitted on January 5, 1950, with a history of enlarged spleen and intermittent hematemesis and melena since April, 1949. On physical examination the spleen could be felt about 2 cm. below the left costal margin. The liver was not palpable. Esophagoscopy and esophagram failed to reveal any esophageal varices. Liver function studies were within normal limits. Hematologic studies revealed no anemia and a platelet count of 200,000.

On January 7, 1950, through a left thoracoabdominal incision, the spleen was isolated. The pressure in the entire portal system, including the splenic vein, the superior mesenteric vein and the coronary vein, was 360 to 390 mm. of water. Accordingly, the spleen was removed and a splenorenal shunt was performed. Immediately after the creation of the splenorenal shunt the pressure in the coronary vein dropped to 260 mm. of water. During the immediate postoperative pressure the platelet count rose to 455,000. The patient was discharged on January 16, 1950.

Discussion of blood in the stools of infants and children would not be complete without a closing notation that, in the rare situation, the etiology of rectal bleeding in later childhood may remain undetected, in spite of extensive and persistent diagnostic efforts. Such was our experience in two patients, aged three and five years, who were admitted for rectal bleeding, carefully studied clinically, and finally subjected to thorough exploratory laparotomy without detection of the cause of their bleeding. Fortunately, such experiences are very few. In most patients the diagnosis can be made and proper treatment may then be applied.

SUMMARY

1. A study of 228 patients with rectal bleeding that were admitted to the Children's Memorial Hospital of Chicago during the years 1948–1953 is presented. During the study five typical clinical syndromes of rectal bleeding were noted.

2. Each syndrome encompassed several clinical entities. The syndromes are described, and the relative frequency of their component clinical entities is given.

3. Case reports illustrating each of the clinical syndromes are included. Some of the more important surgical diseases that cause rectal bleeding are described in detail.

4. It was found that the type and severity of rectal bleeding may be useful in differential diagnosis. Severe rectal bleeding, consisting of bright red blood, frequently indicates a surgical lesion. Milder rectal bleeding is usually associated with lesions that can be treated conservatively. The presence or absence of diarrhea or tarry stools is also of diagnostic value.

REFERENCES

1. Behrer, M. R.: Jejunal Polyposis with Intussusception and Melanin Spots. J. Pediat., 38:641, 1951.
2. Berman, E. J., Schneider, A., and Potts, W. J.: Importance of Gastric Mucosa in Meckel's Diverticulum. J.A.M.A., *156*:6, 1954.
3. Jeghers, H., McKusick, V. F., and Katz, K. H.: Generalized Intestinal Polyposis and Melanin Spots of Oral Mucosa, Lips, and Digits: Syndrome of Diagnostic Significance. New England J. Med., *241*:993, 1949.
4. Ortiz, R., Baffes, T. G., and Potts, W. J.: Gastrointestinal Bleeding in Infants and Children. Quart. Bull., Northwestern Univ. M. School, 27:301, 1953.

707 Fullerton Avenue
Chicago 14, Illinois

CONSTIPATION IN INFANTS AND YOUNG CHILDREN

JOHN LESTER REICHERT, M.D.

This is not a treatise on constipation. It is a discussion of the infant or young child who is brought to the physician because his parents believe that he is constipated.

The complaint of constipation as presented to the physician has many meanings. To some parents it means an interval of more than 24 hours between their child's bowel movements. To some it means that the stool is not soft and mushy, but is "like an adult's." Some parents consider their child to be constipated if they think the movement has too great a diameter or if it occurs in small dry masses. They coin such dramatic terms as "door knob stools," "banana stools" and "rabbit stools." If the bulk of the stool seems too small for the intake of food, many parents think the child is constipated. Some consider a child to be constipated when his stools are firmer or less frequent than ordinary. I refer to parents instead of mothers, because it is usually the father who has the most fixed and mistaken ideas about the process of elimination.

A basic misconception of parents is that constipation is a clinical entity. They have created a syndrome consisting in constipation together with any combination of anorexia, belching or vomiting, abdominal pain, flatulence, listlessness, irritability, headache and vertigo. These symptoms, when not regularly recurring, actually constitute the prodromal or initial picture of an acute febrile disease. But the parents, thinking that lack of adequate elimination is the cause of the condition, "clean him out"; as a result, stress and dehydration aggravate the underlying disease process. Parents often describe a similar clinical picture after a child has been without a bowel movement for 24 to 48 hours. They report that the symptoms disappear as soon as he has had a "good" movement. In these recurring cases the symptoms usually

stem from the child's emotional reaction to the impending ordeal of enema or cathartic, and his recovery can usually be attributed to his relief that the ordeal is over.

To evaluate the significance of constipation as a presenting symptom and not as a clinical entity one must first define the term. One can perhaps best define constipation by taking into account the wide variety of the "normal" in elimination. The infant's or child's stool may vary in consistency from that of mayonnaise to that of putty; the infant's stool tends toward the softer, the child's toward the harder, limit. There may be as many as four evacuations in one day or as few as one in three days. In some children they may be much less frequent. I know of a number of healthy children who average one stool a week. Swenson[6] reports that one normal child had no bowel movement for eight months. He does not say whether he, the parents or the patient was the most uncomfortable. The stool passes normally without pain or blood, but not necessarily without straining. The diameter is of little significance, since stools of unusually large or unusually small diameter occur more often in normal children than in children with atony or stenosis of the terminal bowel.

According to this yardstick, many—perhaps most—of the cases of constipation seen in daily practice are largely or entirely imagined by the parents. But it is just as important to remove the parents' misconception as to eliminate true constipation in the child. Indifference to the parent's misunderstanding only leads them to the misguided use of cathartics, enemas and suppositories, and to continued bad training, all of which eventually result in true constipation. Children who have been misguided into constipation will usually revert to normal when their parents are directed into physiologically and psychologically sound methods of management.

CONSTIPATION IN INFANTS

Except in the neonatal period, the common cause of true constipation in infants is their diet. In the normal breast-fed infant, constipation always indicates underfeeding. The artificially fed baby, too, may be constipated because of inadequate bulk of food. In both breast- and artificially fed babies the constipation may result from total underfeeding, from anorexia and vomiting or from too little roughage in the diet. It occurs when solid foods are withheld or when strained foods are continued too long. In the bottle-fed baby it is probably more often due to an unbalanced diet, especially a diet relatively high in protein or fat, or both, and low in carbohydrate. Formulas enriched with casein or other protein modifier, or with fat, and mixtures low in sugar are common examples. Increasing the sugar to a normal 5 to 7 per cent is usu-

ally corrective. There is a paradoxical reaction to a high sugar content. Constipation is often seen in infants whose formulas contain 15 to 20 per cent of carbohydrate. The stools return promptly to normal when the carbohydrate is reduced to 5 to 7 per cent. I know of no biochemical explanation for this fairly common occurrence.

The stool in constipation of dietary origin is usually hard, and is either of large diameter or is a "rabbit stool." It has a putrid or rancid odor; it is passed with difficulty and is irritating to the baby's skin. The irritation produced in the rectum may lead to the frequent passage of small amounts of stool, a condition which causes the inadequately instructed mother to report that the baby has diarrhea. A variation of this type of bowel movement is the "cork stool," in which a small hard mass is passed with difficulty, followed by unformed feces. The baby on a formula normally has stools that are firmer, less frequent and of deeper color than the breast-fed baby's. When the infant is weaned from the breast, this normal transition is often interpreted by the family as constipation, and leads to ill advised stimulation by laxative foods or cathartics.

All other causes of constipation in the infant are infrequent. In this small group functional or organic obstruction accounts for the majority of cases. *Anal stenosis* due to an anorectal ring is the condition most commonly seen. My experience with it differs from that of Harris et al.[4] I have found it in far fewer than in approximately 15 per cent of newborn babies, which is their incidence. Neither has it been, in my experience, as innocuous a condition as these authors report. Unless routine digital examinations of the rectum are done, it is rarely recognized in the nursery or for a week after the baby has been taken home. The mother then reports that the baby increasingly strains at stool, cries before bowel movement, and passes feces that are pencil- or ribbon-shaped. If the condition persists for a week or more, the stools become less frequent but more liquid, and the baby becomes increasingly unhappy. On inserting the little finger into the anus one gets the impression that a string is tied around the anus just inside the opening. A single, careful dilatation usually restores normal stools and parental serenity. Occasionally symptoms recur in a few days, but they respond to a second, usually easier, dilatation.

All other causes of mechanical obstruction past the neonatal period are rare. They include malrotation of the bowel, agenesis of the myenteric plexus which has escaped the surgeon in the neonatal period, and an abnormally long sigmoid.

Functional obstruction is more often seen. It occurs in infants with anal fissures, proctitis or a meatal ulcer. These are often the aftermath of diarrhea or of a diaper rash. The obstruction is the result of anal spasm due to pain on attempted bowel movement, or from urination

accompanying the bowel movement. These conditions are at once apparent to the clinician who routinely examines that most neglected area of the child, the area between the pubis and the coccyx.

Constipation is rare in the neonatal period. Failure to pass a stool within the first 24 hours is most often caused by a *mucus* or *meconium plug*. If a small enema is given, and the abdomen is gently kneaded, the baby may pass a mottled black to gray-white cast of the bowel from one to ten inches long. It establishes the diagnosis and relieves the obstruction. If a mucus plug is not forthcoming, the presence of lanugo hair and epithelial cells in a smear of the rectal contents will rule out congenital intestinal atresia. Their presence will not eliminate the possibility of intestinal stenosis. Increasing vomiting, visible abdominal peristalsis and fluid levels on an upright roentgenogram of the abdomen confirm the diagnosis of an obstructive lesion.

The pediatrician may ask for a barium enema to demonstrate a malrotation, but it is safer to call the surgeon at this point. While the surgeon is preparing to relieve the obstruction surgically, one may consider, academically, the usual causes of obstruction. In addition to malrotation they include the following: congenital intestinal atresia, the location of which is suggested by the pattern of fluid levels on upright roentgenogram; agenesis of the myenteric plexus, with intermittent obstruction; duplication of the bowel; and meconium ileus, in which intra-abdominal calcium deposits can be demonstrated by roentgenogram. Abdominal distention occurs early in meconium ileus, but differs from other causes of obstruction in that fluid levels are not seen in the upright film.

CONSTIPATION IN EARLY CHILDHOOD

By far the most common cause of constipation after the first year is *faulty habit*. Faulty habit usually results from the child's resistance to coercion in bowel and bladder training. We are just beginning to convince parents that it is no physiologic or social stigma for a child to soil and wet himself in his second year. We still have to convince many parents that the normal method of teaching control is to get the child to associate the sensation of an impending bowel movement with the toilet seat. Not until the beginning of neuromuscular control, which is said usually to occur between 12 and 18 months of age,[5] does the baby recognize this sensation. Evacuation of stool and urine is almost always an unconscious act up to a year and may be so up to the age of 30 months.

Taking the child from his play during this period and confining him to an uncomfortable and insecure toilet seat can have no meaning to him except to create a feeling of unjustified interference with his nor-

mal activities. When in the course of his physiologic and emotional maturing he learns to sense an impending bowel movement, he includes the impulse in his negative reaction. He then holds back the movement until he has been taken from the seat, whereupon he promptly passes it, to the obvious exasperation of his parents. Their exasperation further increases his tensions and his negative attitude, and he restrains his impulse until he can pass the stool out of sight of the family.

Physiologically, it is this holding back that deadens the normal reflex to peristalsis and causes the stool to be retained in the lower bowel, where it rapidly loses its fluid content. When pressure finally forces the large hard stool past the anus, evacuation is accomplished with pain, with resulting anal spasm and functional obstruction to passage of the stool. Eventually, after repeated insults, the threshold of the reflex mechanism is permanently raised, and the spastic reaction gives way to atony. During the spastic stage the stool is hard, pencil- or ribbon-shaped, or of the rabbit type. It may be passed every two to four days, or there may be frequent, small, often involuntary evacuations. In the atonic stage the stool has a large diameter.

The same picture may develop if the child ignores or resists the stool for any physical or psychologic reason. It is seen commonly in the older preschool child who does not want to leave his play and in the child who does not take time for a complete evacuation because he does not want to be late for school, a habit referred to as dyschezia. Conversely, in the child who delays his departure from the house by prolonging his evacuation time because he is unhappy at school, severe constipation may develop on the basis of an emotional block.

In both the spastic and atonic stages of severe degree encopresis, or involuntary soiling, may develop. It is sometimes confused with the incontinence of children having neurologic lesions, such as are seen in meningocele and in other involvements of the spinal cord. Swenson[6] points out that almost always a child with a spinal lesion also lacks bladder control. He distinguishes severe cases of habit constipation from megacolon. With megacolon the constipation is present from birth, and there is periodic abdominal distention, but no fecal incontinence.

Constipation of dietary origin is less common in childhood than in infancy. By the age of one year the child has usually made an adjustment between intake and elimination. When constipation occurs, it is commonly associated with acute illness or other cause of temporary anorexia. An exception is seen in children whose parents do not know that there is a normal decrease in food intake in the second year coincident with the normal slowing in the rate of gain. These children are given excessive amounts of milk to make up the supposed deficit. They constitute the "at least he's getting his milk" group of constipated children.

Books on child care written for parents have aided the physician greatly in decreasing the incidence of cathartic constipation. But one still commonly sees children whose normal reflex to evacuation has been exhausted by overstimulation from the repeated use of suppositories, enemas and cathartics. One must guard against too tolerant an attitude toward these artificial aids. A similar but temporary exhaustion often occurs after an attack of diarrhea or from too vigorous treatment of the diarrhea.

I have rarely found constipation to be caused by food allergy, despite reference in the literature to its occurrence.[2] Diarrhea, in my experience, is the rule.

PSYCHOLOGIC FACTORS IN CONSTIPATION

Psychologic factors play a prominent role in the development of constipation.[3, 5, 6] Bell and Levine[1] recently reported 22 cases in which constipation was relieved by measures aimed at removing a child's repulsion to fecal matter. I recently saw a child who would not have a bowel movement unless she had on a certain nightgown, another who would defecate only when standing up, and a five year old boy who was secretive about his bowel elimination and hid the stool between the pages of his father's law books. This type of behavior obviously indicates a fundamental emotional maladjustment.

Some cases are probably based on the unconscious suggestion by adults that feces are messy and disgusting. In such cases, finger painting, as advised by Bell and Levine, is an ingenious way of removing the impression that being messy is bad. Some cases stem from more complex causes. But it does not follow that these situations call for immediate exhaustive psychologic investigation. The child who defecated standing up, sat down to stool a few days after an aunt who lived with the family had gone on a vacation; the girl with the nightgown complex responded to a bribe of candy after each evacuation; and the boy who found a new use for law books stopped his quaint custom after his father had transferred the feces to the boy's own books. In none of these cases was the underlying cause discovered or seriously sought for. Improvement occurred when the family tension was relieved, in the first case by the departure of the aunt, in the others by the assurance that these actions did not indicate mental derangement. The use of the simple measures gave the parents an outlet and ended the violent disapproval to which the children were subjected. I do not underestimate the value of competent psychiatric investigation in persistent cases, but most children seen in private practice respond satisfactorily to simple measures aimed at relieving the fears of the parents and removing the onus from the child.

CLASSIFICATION

A complete classification of the causes of constipation has little place in this discussion. The important conditions to be considered in a patient with the presenting symptoms of constipation have already been mentioned. But in order to include syndromes in which constipation may rarely be the prominent symptom, I offer the following tabulation.

I. DIETARY IRREGULARITY* (small formed or rabbit stools, or alternating soft and hard stools)
   A. Inadequate intake, underfeeding, anorexia, vomiting
   B. High protein and/or high fat with low carbohydrate
   C. Too little roughage; solids started too late in infancy; strained foods too long; food aversions

II. SPASTIC CONSTIPATION (rabbit or ribbon stools)
   A. Faulty habits of elimination*
      1. Errors in training, especially coercion
      2. Ignoring the urge
      3. Overuse of cathartics, enemas, suppositories
   B. Local pain; fissures, hemorrhoids, proctitis, meatal ulcer, intestinal parasites
   C. Spastic colitis (?)

III. ATONIC CONSTIPATION (stools of large diameter; infrequent; may be soft)
   A. Late stage of spastic,* especially when resulting from faulty habits
   B. Following acute diarrhea;* temporary
   C. Emotional block*
   D. Autonomic imbalance
      Megacolon*
      Postoperative anal stenosis*
      Myenteric plexus agenesis
   E. Metabolic diseases, rickets, mongolism, hypothyroidism, celiac syndrome, thiamine deficiency (?)
   F. Neurologic disease: meningocele and other lower motor neuron dysfunction

IV. OBSTRUCTION
   Congenital gastrointestinal atresia and stenosis
   Intussusception, tumors and other acquired causes of obstruction

TREATMENT

The Family

As has been said, most of the children brought to the physician for constipation need only to be freed from the fears and subsequent mismanagement of their anxious parents. Often the only treatment necessary is the family's clear understanding of the normal limits of defecation. To understand normal variations, the parents must have some knowledge of the normal physiology of bowel elimination. Equally important, they must appreciate the psychologic implications of constipation. To help them, their physician often can more effectively cite examples than discuss psychologic principles. The parents of the child whose constipation disappeared when the aunt left home were convinced that family tensions were the basic factor in the child's difficulty.

* Conditions in which constipation is usually the presenting symptom.

Citing this case and similar ones to other parents has helped them to evaluate their own families' emotional situation.

The Patient

Regulation of the Diet. This will correct almost all cases of constipation in the infant. It is just as important in the young child, but at this age it is complicated by poor bowel training. In practice, the corrective procedures and, roughly, their sequence are as follows:

1. Increase the quantity of food if it is inadequate. Mild constipation is often the first indication of a grossly inadequate diet.
2. Increase the carbohydrate if the volume of food is adequate or if making it adequate does not correct the constipation. But remember that excessive amounts of carbohydrate may aggravate constipation.
3. Change to slowly absorbed carbohydrate such as malt, dextrins and other polysaccharides. A valuable product in treating constipation throughout infancy and childhood is a malt soup extract available as a syrup or powder. One teaspoon, gradually increased as necessary, can be added to the formula or to fruit or cereal.
4. Reduce the fat, especially if the stools are greasy or rancid, or contain soap curds. Reducing fat by using skimmed milk or a skimmed milk powder has the further advantage of increasing the appetite and thereby increasing the bulk of the diet.
5. Add prune juice, a time-honored method known to all mothers.
6. Increase bulky foods, such as fruits, leafy vegetables and bran. Since anorexia is often a part of the picture, this is not always easy. The use of a homemade *fruit loaf* is helpful. It is prepared as follows:

A pound of mixed dried fruits, such as raisins, apricots, prunes, figs and dates, are put through a meat grinder together with enough molasses or brown sugar to make the mass cohesive. Six senna leaves can be crushed and mixed into the mass for the first loaf or two. The mass is molded and rolled in powdered sugar. It is kept cold, and one or more slices are given for dessert.

Adding *methyl-cellulose,* a hydrophilic colloid, to the diet effectively increases the bulk and the "smoothage" of the intestinal content. Since it is not assimilated and is completely bland, it reaches the colon, where its mass stimulates propulsive peristalsis without increasing segmental spasm. For this reason it is sometimes ineffective in cases of marked atony of the bowel. Here the fruit loaf, or a combination of the two, is more adequate.

Oatmeal, leafy vegetables, prunes and honey are usually thought of as laxative foods. But there are many individual variations. A detailed knowledge of the food idiosyncrasies of a child is particularly valuable in managing present or potential allergic reactions. It also aids in the management of bowel function. Many mothers learn this individual

response by trial and error. It can be more readily and accurately determined if each new food added to the infant's diet is given for three successive days and if only one new food is started at a time.

Most infants can be shifted from formula to whole milk without disturbance, although usually the stools become firmer and less frequent. Occasionally constipation occurs with the change. This minor problem is eliminated by adding the carbohydrate of the formula to the milk and gradually reducing it.

Correction of Faulty Habits. This is a problem in discipline. Firm kindness and persistence are important. Six months is not a long period for establishing good habits. Both parents and physicians must follow the principle that applies to all disciplining of children, that of guidance and not of domination.

Most faulty habits of elimination can be avoided if the proper guidance is given during the period of bowel training. No measures should be instituted until there is a definite, conscious neuromuscular connection between the child's brain and lower bowel. When this connection is established, the baby indicates his consciousness of an impending evacuation by some definite act or signal. He may assume a characteristic position, become very quiet or "get that look on his face." That is the signal to place him on the toilet seat. After a few such experiences the sensation of the seat will in itself stimulate massive peristalsis and evacuation.

Bladder control should not be attempted until bowel control is well established.

Mechanical Aids. Although mechanical aids have a place in treating constipation, they are largely temporary expedients. They are harmful if used routinely, since they blunt the normal response to feces in the rectum and are quickly habit forming. But there is no harm in using a soap stick or glycerin *suppository* in a child who has had no bowel movement for 48 to 72 hours because of sudden reduction in intake, as occurs in acute febrile illness. A suppository relieves the parent and may give some relief to the patient. Placing the suppository halfway into the rectum is physiologically inadequate and psychologically wrong. Using the oiled finger or a rectal thermometer to push it in, one should insert the moistened suppository into the anus past the sphincter. As soon as it is entirely in the rectum, it will turn crosswise and cannot be readily expelled. The child should then be left alone until the melting suppository both lubricates the rectum and, by irritation, stimulates contraction. In this way, as little connection as possible is made in the child's mind between the suppository and the resulting evacuation.

A *cleansing enema* serves much the same purpose as a suppository, but is more vigorous, since it stimulates peristalsis both by mechanical irritation and by distention. When the child is febrile, it has an advan-

tage of reducing the fever and supplying him with extra fluid by absorption from the colon. A bland solution, as normal saline, is the fluid of choice, using from 8 ounces in the infant up to 1 quart in the school age child. An enema bag is preferable to a bulb syringe, since it causes less anal irritation. The bag should not be higher than 2 feet above the level of the anus to avoid too rapid and painful distention of the bowel. The solution should be given at body temperature.

Retention enemas of mineral or olive oil are helpful as an immediate aid in reducing the pain of passing a hard fecal mass. A common problem is the child who holds back because he remembers previous painful evacuations. Such retention occurs during and for a surprisingly long time after proctitis, anal fissures or any other cause of anal pain. The following mixture, used daily for not more than a week, is helpful:

Benzocaine*	2.0	gm.	(32 grains)
Protargol	0.16	gm.	(2½ grains)
Lanolin	6.0	gm.	(1½ drams)
Glycerin	6.0	cc.	(1½ drams)
Liq. petrolatum q.s. ad	30.0	cc.	(1 ounce)

Add 1 teaspoonful to 1 ounce of mineral oil and inject through a bulb syringe at body temperature once daily at the usual time of evacuation.

In using a rectal bulb syringe one must always keep the tip of the syringe lower than the bulb in order to avoid injecting air into the rectum. The best method is to have the child lie on his abdomen. This position, by enabling the parent to separate the buttocks and visualize the anus, also insures a gentle and painless insertion. Dietary and training measures should always be part of the management to avoid undue repetition of oil injections.

Abdominal massage, aimed at moving fecal content along the colon and stimulating peristalsis, has a limited role in treating atonic constipation. Pressing the thighs onto the abdomen is a time-honored aid in infants. It puts the infant in the normal squatting position for bowel movement and probably has some psychologic value.

Mechanical aids must be used routinely to produce bowel movement in neuromuscular dysfunction, as in meningocele. Saline or tapwater enemas are usually used. They should be restricted to the longest interval compatible with the child's comfort. If properly advised, parents find that the artificial production of a bowel movement every four to seven days is adequate.

Cathartics have no place in treating constipation in children. It is illogical to irritate the entire intestinal tract in order to stimulate its terminal 2 inches. Mineral oil, alone or combined with agar or methyl-

* If pain, on defecation, is severe, *butyn sulfate* (32 grains to a 1 ounce mixture) can be used in place of benzocaine. The mixture should be well triturated.

cellulose, has a limited place in a training program. Since mineral oil will absorb vitamins and prevent their assimilation, at least one meal should intervene between the ingestion of the daily vitamin supplements and the administration of the oil. The leaking of oil from the anus is often an objection. It may lead the parent to change to a cathartic, which defeats the purpose of the treatment. Petrolatum mixed with honey or molasses in a kitchen blender is usually well taken, does not leak, and is not nearly as repulsive as it sounds.

Despite physicians' rejection of cathartics, the arbitrary banning of all laxatives, including such mild ones as milk of magnesia and aromatic cascara, is not good practice. Used occasionally with the physician's approval, they relieve the parental emergency, do the child no harm, and save face for the physician, since the parent will probably give them anyway. But the parent should be told that the evacuation from a cathartic or enema may so completely empty the bowel that it will take two to four days for it to refill, and that they can expect the absence of a bowel movement for several days.

Antispasmodics are of value in managing spastic constipation, when segmental contractions have largely replaced propulsive peristalsis. Belladonna and its derivatives are commonly used. Novatropine methylbromide (Novatrin) has a low toxicity. In doses of $\frac{1}{100}$ to $\frac{1}{25}$ grain (0.65 to 2.5 mg.) every four hours or with meals it is an effective aid and is without side effects. It is often combined with phenobarbital. Medication in spastic constipation should be only an accessory to the essential measures of diet and the correction of contributory psychologic difficulties.

Parasympathomimetic drugs such as Mecholyl, in doses of 0.3 to 0.65 mg. ($\frac{1}{200}$ to $\frac{1}{100}$ grain) orally twice a day, or Prostigmin Bromide, 3.75 to 7.5 mg. ($\frac{1}{16}$ to $\frac{1}{8}$ grain) orally three times daily, are indicated in cases of atonic constipation which do not respond to increased bulk and massage, and to an attempt at removing emotional blocks. As with all drug therapy in constipation, they should be used for a limited time and in decreasing dosage. Constipation should always be corrected gradually. The condition is at most a nuisance, never an emergency. If it is overtreated, the resulting diarrhea can be serious.

SUMMARY

Constipation in probably the majority of cases in infants and children exists largely or entirely in the minds of the parents. Management in this large group must be directed primarily at the parents. True constipation in infants usually results from an inadequate diet. In young children it is most commonly due to faulty habits. The essentials of management are therefore parent education, diet therapy, proper train-

ing in habits of bowel evacuation and understanding and counsel in the emotional problems of the child and his family. Drug therapy plays a minor role. Less common causes of constipation are mentioned. The only added points in the management of these cases are those that deal with the treatment of the cause.

REFERENCES

1. Bell, A. I., and Levine, M. I.: The Psychologic Aspects of Pediatric Practice. Pediatrics, *14*:259, 1954.
2. Brenneman, J.: Practice of Pediatrics. Hagerstown, Md., W. F. Prior Co., Vol. 7, Chap. 13, p. 28.
3. Garrard, S. D., and Richmond, J. B.: Psychogenic Megacolon Manifested by Fecal Soiling. Pediatrics, *10*:474, 1952.
4. Harris, L. E., Corbin, H. P. F., and Hill, J. R.: Anorectal Rings in Infancy: Incidence and Significance. Pediatrics, *13*:59, 1954.
5. Huschka, M.: The Child's Response to Coercive Bowel Training. Psychosom. Med., *4*:301, 1942.
6. Swenson, O.: Classification and Treatment of Children with Severe Chronic Constipation. Am. J. Surg., *86*:497, 1953.
7. Vignec, A. J., and Mitty, V. C.: Treatment of Constipation in Infancy and Childhood. J. Pediat., *40*:576, 1952.

1791 West Howard Street
Chicago 26, Illinois

MENSTRUAL PROBLEMS OF THE ADOLESCENT

JOHN W. HUFFMAN, M.D.

Delay of the menarche, infrequent menstruation, profuse or prolonged menstruation and menstrual pain are among the most frequently presented adolescent gynecologic complaints. There is an understandable tendency to delay investigative procedures when a girl in her early teens presents some form of menstrual irregularity. This is due, in part, to the difficulty which is often present in establishing an accurate diagnosis. It is also the result of the realization that many of the problems may right themselves spontaneously. It is hoped that correcting some of the disturbances which cause menstrual problems in the adolescent girl will render her healthier during her period of growth.

CAUSATIVE FACTORS

There is great variation in the age at which different individuals enter the period of sexual development. When somatic development does not keep pace with chronologic age, the growth and, therefore, the function of the genitalia will be more closely correlated with body growth than is the subject's age in years. Asiatic, Negro, American Indian, Mediterranean racial groups and Jewish girls tend to menstruate earlier than do Scandinavian, Anglo-Saxon and Central European groups. The climate in which the girl lives is less important than is her racial and familial background as related to the age at which she begins to menstruate. Moving to a distant place may be a potent factor in causing cessation of menstruation for many months.

Menstruation will not occur when the hypophysis fails to produce sufficient gonadotropin to activate the normal ovary. A fault in the hypophysial-ovarian-endocrine mechanism which creates the physiologic

bleeding of menstruation is by far the commonest disturbance responsible for abnormal bleeding. The thyroid may act through its alteration of hypophysial tropic hormones or directly upon the cellular metabolism of the ovary. Both hypothyroidism and hyperthyroidism, the first more often than the second, may be associated with infrequent periods and dysfunctional flow. Congenital adrenal hyperplasia is the commonest endocrine disorder giving rise to menstrual failure associated with virilization. Amenorrhea is almost invariably one of the symptoms of adrenal cortical hyperactivity.

There is good evidence that nutritional factors influence hormonal metabolism, although the role of vitamins in estrogen metabolism is open to question. Systemic disease, particularly of a chronic or debilitating type, may sufficiently damage ovarian development to produce a lasting, depressing effect upon ovarian function. Hypochromic anemia, thrombocytopenic or nonthrombocytopenic purpura may be factors producing excessive bleeding. Chronic exhaustion and fatigue rivals real illness in the manner in which it interferes with the delicate mechanism causing menstruation.

Aggravation of psychic and emotional conflicts may be revealed through menstrual irregularities. The presence of cerebral hypothalamic hypophysial pathways explains why emotional and psychic stresses may markedly disturb the rhythm of menstruation through centrally induced alterations in hypophysial function.

Organic disease of the genitalia as a cause of uterine bleeding is unusual in the first half of the second decade. Every kind of genital neoplasm, with one or two exceptions, has been reported as occurring during adolescence; the number of most varieties is small. Feminizing tumors characteristically cause an increased amount of flow and irregularity of menstruation. Pelvic endometriosis is almost unheard of in girls under 17 years of age. Residual pelvic inflammatory reactions during adolescence require consideration only in exceptional cases.

Increased heparinoid substances in the circulating blood explain many cases of dysfunctional bleeding in adolescence. The relationship and manner in which they affect the ovarian and uterine physiologic mechanisms and cause abnormal bleeding are unknown.

Developmental defects are the basis for some cases of menstrual failure. While not true menstrual failure, an imperforate hymen may prevent the escape of menstrual blood. Anatomic defects rarely cause menstrual pain. There is little evidence to support the contention that congenital displacements of the uterus are factors in the menstrual disorders seen in adolescence. Acquired displacements of the uterus are not apt to be agents in producing uterine dysfunctions. They are rarely encountered in the adolescent.

DIFFERENTIAL DIAGNOSIS

Examination is essential in making a differential diagnosis. It includes an evaluation of the patient's general state of health and a search for endocrine and developmental congenital disorders. Endocrine disturbances may be revealed by deviations from the normal in height, weight, height-span relationship, the condition of the hair, eyes, skin and abnormalities of body contour and fat distribution. Examination of the genitalia determines whether there is a correlation of genital and somatic growth, and whether there are congenital anomalies or organic genital disorders.

Amenorrhea

The adolescent girl's failure to menstruate takes one of two forms: either she has a delay in the menarche or, after one or more periods, she has no others or long intervals of time elapse between periods. The average age for the menarche is 13½ years. Deviations from that age are so frequently followed by normal sexual development that girls whose menstrual periods begin when they are ten years of age or are delayed until they are 16 years of age are considered to be within normal range. Absence of the menarche after the age of 16 is rarely normal; however, it may be merely an evidence of slow maturation. Irregularity of menstruation is common for some time after the menarche. Most girls have established fairly regular cycles by the time they are 17 years of age. It is unwarranted meddling to subject a 14 year old girl who has not menstruated, but is otherwise normal, to extensive examination. If her menarche has not occurred by the time she is 15, limited efforts should be made to exclude some of the commoner causes for primary menstrual failure. Absence of the menarche after the age of 16 is an indication for a thorough examination.

Pregnancy. Pregnancy rarely becomes a factor in the differential diagnosis of menstrual failure. It is extremely unlikely that a girl would become pregnant at the ovulation preceding her first menstrual period. Many girls have a period of months and even years after the menarche when menstruation follows an anovulatory cycle. This would explain why pregnancy during adolescence is rare, even among primitive tribes in which coitus begins at an early age.

Constitutional Amenorrhea. Examination of the girl whose menstrual failure is really a "constitutional amenorrhea" contributes to the diagnosis so far as it excludes systemic, endocrine, developmental and genital disorders. Usually the only positive findings are those which suggest some delay in somatic development.

Ovarian Factors. Absence of menstruation caused by ovarian factors

is the result of ovarian failure, ovarian agenesis or premenarchal bilateral ovariectomy.

When *ovarian failure* is complete, there is a eunuchoid configuration with an increase in the length of the long bones and, therefore, an undue increase in the height. There is an increase in arm span as related to total body length. The breasts remain small. There is normal growth of axillary and pubic hair. The genitalia evidence no sign of maturation other than some enlargement of the labia majora. The *p*H of the vaginal fluid remains alkaline. Vaginal cytosmears show no cornification of the vaginal cells. Hormonal assays reveal an absence or low level of estrogen and absence of pregnanediol, an increase in the follicle-stimulating hormone levels and normal 17-ketosteroid concentrations. Uterine bleeding will not follow the administration of large doses of progesterone, for there is no endogenous estrogen to prime the endometrium. The genitalia will develop and withdrawal uterine bleeding will occur when estrogen and progesterone are administered together in a cyclic fashion.

When ovarian failure is partial, the menarche is usually delayed, the adolescent having one or several widely separated menstrual periods. Examination reveals a feminine body contour. Development of the mammary glands and growth of axillary and pubic hair tend to be relatively normal. The genitalia and areolas of the breasts reveal subnormal estrogenic stimulation. Some development of all three does occur, but it does not keep pace with the somatic or chronologic age. The cytosmear contains scattered cornified cells. The administration of large doses of progesterone over a period of several days may be followed by withdrawal bleeding. Such a response to progesterone indicates that enough gonadotropin is produced by the hypophysis to induce partial follicular development and some estrogen elaboration by the ovary. It also reveals the ability of the endometrium to respond in a normal fashion to the ovarian hormones.

Failure to menstruate is one symptom of, and failure of genital maturation one sign associated with, *ovarian agenesis*. The latter itself is but a part of a widespread developmental defect. The syndrome is characterized by a failure to attain normal height, which may approximate dwarfism, some, but not an exaggerated, delay in the bone age and a tendency to various congenital anomalies, the most evident of which is webbing of the neck. The breasts do not develop. Genital and axillary hair growth is normal. There is a marked increase in the follicle-stimulating hormone titer.

Hypophysial Dysfunction. When menstrual failure is a symptom of a hypophysial dysfunction which occurred prior to the time of sexual differentiation and somatic growth, it may be overshadowed by other disturbances. Not only is there an absence of genital growth, but bodily growth does not take place. The breasts do not develop, axillary and

genital hair does not appear, and there is no acquisition of a feminine structural configuration. Hormonal assays reveal a decrease in the output of the follicle-stimulating hormone, the 17-ketosteroids and low or absent estrogen titers. There is no cornification of the vaginal epithelium.

Hypopituitarism. Hypopituitarism during adolescence creates conditions which are the result of an inadequate production of all the tropic hormones. Amenorrhea is but one facet of its symptomatology. The elaboration of the gonadotropins is often affected before there is a decrease in the production of the other tropic substances. For that reason menstrual failure may be the only sign, except for inadequate genital development, of impaired anterior hypophysial function.

Hypothyroidism. The adolescent whose menstrual irregularity is the result of *hypothyroidism* gives a history of having menstruated at approximately the expected time with infrequent periods thereafter. Frequently she does not show the classical symptoms of clinical hypothyroidism. In many instances the establishment of normal menstrual cycles after the administration of thyroid extract is the only significant indication that thyroid insufficiency was the causative agent.

Systemic Disorders. Amenorrhea which accompanies systemic disorders and debilitating diseases is usually only one symptom of the patient's illness. Rarely, a history of a serious illness prior to the period of sexual development and ovarian maturation will explain the adolescent's menstrual failure. Anemia and tuberculosis are thought of whenever a listless, physically underpar girl does not menstruate or menstruates only infrequently. Obesity and the history of bad eating habits deserve consideration in the diagnosis.

Psychic and Emotional Agents. It is difficult to establish a diagnosis of psychic and emotional agents as the causation of menstrual failure. In most cases the diagnosis is essentially a matter of excluding organic and dysfunctional agents.

Developmental Factors. Developmental factors which interfere with the onset of menstruation require consideration. Laparotomy is occasionally indicated in those girls in whom the question of the formation of a feminine genital tract must be considered. Aplasia of all or part of the genital canal may occur with normal ovarian and pituitary activity. When there is partial atresia, there may be bands or obstructive partitions which prevent the egress of menstrual flow. The adolescent girl gives a history of having experienced monthly or recurrent periodic lower abdominal, cramping pain suggesting menstruation, but without menstrual flow. When cryptomenorrhea is caused by an imperforate hymen, the hymen appears as a bulging, dome-shaped, purplish tumefaction distending the vulvar tissues. The external genitalia are otherwise well formed. Genital growth and somatic growth are normal.

Adrenal Disorders. Menstrual failure associated with adrenal disorders

is usually one of the symptoms of congenital adrenal cortical hyperplasia, androgen-producing adrenal tumors or Cushing's syndrome. Menstrual failure and virilization are common to all three.

Congenital adrenocortical hyperplasia is characterized by contrasexual congenital deformities of the genitalia. It produces slowly developing virilization during childhood with rapid masculine somatic growth and accelerated virilization at adolescence. There is an increased 17-ketosteroid titer which falls in response to cortisone.

Androgen-producing tumors of the adrenal cortex, like congenital adrenocortical hyperplasia, induce hirsutism, clitoral hypertrophy, precocious somatic development, failure of genital development, inhibition of ovarian activity and menstrual failure. There is rapid virilization at any age at which such a neoplasm develops in any patient. These girls have a normal female genital architecture at birth. With the growth of the tumor there is a greatly increased output of 17-ketosteroids; the titer does not respond to cortisone.

The symptoms of *Cushing's syndrome* are varied. The clinical picture in an individual case depends upon the types of adrenocortical hormones which are elaborated in a greater than normal amount. Failure of genital growth, absence of menstruation, failure of normal skeletal growth and retarded bone age are almost always part of the symptomatology when this condition is encountered in the adolescent female. Hirsutism, clitoral enlargement and increased 17-ketosteroid titers are usually marked. Several or all of the following signs or symptoms are usually present and are significant in the diagnosis: obesity, a diabetic glucose tolerance curve, resistance to insulin, osteoporosis, hypertension, polycythemia, red abdominal striae, increased capillary fragility and signs of disturbed electrolytic balances.

The differential diagnosis of delayed or absent menstruation associated with virilization must also include consideration of the following: the intersexed or pseudohermaphroditic male who is erroneously believed to be a female; the bisexed or truly hermaphroditic person whose external form is predominantly female, but who does not menstruate; and the female who complains of menstrual failure and presents some signs of virilization, yet does not give evidence of adrenocortical disorders.

Cases are occasionally encountered in which menstrual failure and hirsutism are problems, and yet the patient shows few or no other evidences of virilization. Her childhood history is one of normal somatic and genital growth. During adolescence an excessive growth of hair develops which has a masculine distribution, and she has infrequent menstruation. Usually there is no other evidence of excessive androgenic activity. An exploratory laparotomy, which is often done in such cases, frequently discloses large, pale, polycystic ovaries such as those described

by Stein.[22] There is usually no explanation for the cause of infrequent menstruation and hirsutism in this group. These girls rarely show any other symptoms or signs suggesting either adrenocortical hyperplasia or Cushing's syndrome.

Pneumoperitoneum, exploratory laparotomy, skin biopsy, urograms and exploration of the adrenals are sometimes diagnostically helpful in differentiating among the several conditions in which absent or infrequent menstruation is associated with virilization.

Dysmenorrhea

The adolescent whose presenting complaint is dysmenorrhea has usually been menstruating for several years. If hers is the typical case, she did not experience pain with her first period, nor did it accompany the several periods which followed the menarche. She tends to be physically healthy and to have no other complaints. Usually she presents no signs of somatic or genital disorders. Her periods are often relatively regular as regards rhythm and normal as regards the amount and duration of the flow.

Dysmenorrhea is a symptom rather than a specific disease. During adolescence it is almost invariably primary in type. Primary dismenorrhea is defined as painful menstruation for which there is no discoverable cause. The pain which accompanies secondary dysmenorrhea is created by an organic disorder or anatomic defect. The differential diagnosis is a matter of first excluding organic and anatomic entities and then of considering the several presumptive factors believed to play a part in the etiology of primary dysmenorrhea.

The history, the girl's age and the absence of demonstrable pelvic pathosis will usually exclude organic lesions as causative agents. The diagnosis of *uterine hypoplasia* during adolescence should be made with hesitancy. Remember that the uterus of the adolescent girl is normally not as large as it will be when she has fully matured. Markedly hypoplastic uteri, such as are found with severe or complete ovarian failure, are, of course, not factors in dysmenorrhea, for such uteri do not menstruate. *Congenital stenosis of the genital canal*, particularly of the cervix, rarely causes pain with menstruation. Actually, it is most unusual to demonstrate any anatomic obstruction of the cervix which would interfere with the egress of menstrual flow unless the cervix has been traumatized or infected. Such trauma and infection are extremely uncommon in adolescent girls. Distention by menstrual fluid in a rudimentary uterine horn which is not connected with the uterine cavity may simulate a true dysmenorrhea. Such cases are unusual. The diagnosis is established by the presence of an intrapelvic fluctuant tumor mass and also by the presence of recurrent lower abdominal pain at the time of

the period. If the condition has gone on for many months, the mass may assume large proportions.

Pelvic peritonitis and acute *infections of the internal genitalia* may occur during childhood and adolescence as a complication of a systemic disease. In rare instances distortion and fixation of the uterus and adnexa following such an infection are etiologic factors in dysmenorrhea, which begins with the menarche and persists into adult life.

The fact that most girls do not have dysmenorrhea until they have had a number of periods is explained on the basis that the first several menstrual cycles are anovulatory ones. Dysmenorrhea rarely accompanies *anovulatory menstruation*. It might be assumed, therefore, that primary dysmenorrhea is a manifestation of a deranged mechanism which is subject to the ovarian hormones. Actually the etiology of primary dysmenorrhea is unknown. The best evidence is that it is caused by a uterine muscular dysfunction or a uterine circulatory disturbance.

The pain which occurs with primary dysmenorrhea may precede the flow by several days; it may occur with the onset of bleeding or not until after the period has been well established. It may last for only a few hours or may persist throughout the period. It varies from a severe, incapacitating, acute distress, which requires opiates for relief, to lesser annoyances which are controlled by simple analgesics. Usually it is accompanied by malaise, backache, headache, leg ache, and often nausea and vomiting. Typically, the discomfort is cramping, sharp, colicky, recurrent and contraction-like in character. In secondary dysmenorrhea the discomfort is more often aching, dull, but persistent. It is much less likely to be associated with the molimina which accompany primary dysmenorrhea.

Certain conclusions may be drawn from studies of adolescents who have kept basal body temperature charts: namely, in adolescence dysmenorrhea occurs with an ovulatory cycle. Anovulatory cycles, created by hormonal therapy in dysmenorrheic adolescents, are almost invariably accompanied by an absence of or a markedly diminished discomfort. The implication would be that relatively normal ovarian function, rather than dysfunction, is a prerequisite for primary dysmenorrhea in adolescence. Furthermore, there is evidence that an ovarian substance, closely related to the hormone relaxin, is capable of inhibiting spasmodic uterine contractions. Its effect in relieving primary dysmenorrhea in adolescence would support the assumption that the adolescent's menstrual pain is a functional uterine disorder not specifically related to ovarian hormonal imbalances.

Overwork in school, a too active social life outside of school, insufficient rest, undue fatigue, a sedentary indoor life and inadequate exercise all tend to aggravate menstrual discomfort through increasing *nervous tension* and reducing *emotional stability*. Though constitutional

disorders and ill health are contributory factors, they are not, by any means, main factors in most cases. Chronic *pelvic congestion* induced by erotic stimuli is an important element in the causation of dysmenorrhea in the adolescent who is developing strong heterosexual interests.

Emotional stress and *psychic trauma* unquestionably play large etiologic roles in a great many cases. Many different types of emotional and psychic problems can be cited as examples of situations that contribute to the development of dysmenorrhea. They include an oversolicitous mother, neurotic parents or older siblings, family conflicts, competition with siblings, and stresses or maladjustments in school, social and sexual relationships. The commonest of these is the emotionally unstable mother who inculcates in her daughter the idea that menstruation is a period of ill health. Often she has suffered from incapacitating dysmenorrhea. Frequently the girl's monthly pain represents an attempt to deviate attention from a more dominant sister or brother. It is also likely to be an opportunity for her to escape temporarily from the competition of the outside world into the sympathetic environment which her condition creates. Psychiatric evaluations are not necessary unless the emotional problem is an occult one or is one which the physician feels requires specialized management.

Lowered pain thresholds secondary to either systemic disorders or psychic instability have been alleged to be factors in primary dysmenorrhea. It is quite as logical to assume that the majority of normal girls would have a decrease in their pain threshold if they were forced to anticipate recurrent episodes of severe pain every 28 days.

Excessive Menstruation

When the adolescent girl's menstrual problem is profuse or prolonged menstruation, it is necessary to differentiate between the bleeding which is caused by an organic disease of the genitalia and that caused by a dysfunctional state. Normally her flow should not begin more often than every 23 days, it should not last more than seven days, nor should it require more than six ordinary perineal pads to control any one day's flow. It is abnormal if it is prolonged, even though profuse, moderate or slight in amount. It may be of normal duration and yet be accompanied by profuse hemorrhages. It may start with the first period, or it may follow the establishment of a number of normal cycles. Often it follows a period of amenorrhea.

Profuse or prolonged menstruation during adolescence is most often dysfunctional in origin. It is a symptom of an endocrine disturbance, a systemic disorder, an abnormal nutritional state, the presence of some psychic problem, or an increase in circulating heparinoid substances.

Endocrine Disturbances. Endocrine disturbances are the commonest

factor in the etiology of excessive menstruation in adolescence. The diagnosis depends upon excluding other causes. A continued, moderate flow with alterations in the amount of flow from day to day is probably the result of a continuous elevation of the estrogen titer with an occasional drop in the amount of estrogen produced. A sudden, profuse flow may be a sign of a sudden drop in the estrogen level. Spotting bleeding before or after menstruation suggests an imbalance between estrogen and progesterone with poor progestational elaboration. Most bleeding episodes which are dysfunctional in origin are painless and usually are a signal of an anovulatory ovarian cycle. The bleeding may come from any type of endometrium. The genitalia are usually normal as regards their development. The girl whose flow is associated with increased estrogen will often show evidences of advanced somatic and genital maturation. There is an accentuation of the secondary sexual characteristics and an acceleration in the growth of the genitalia. The vaginal depth and diameter approximate those of the adult or older girl. The uterus, although small, is adult in type. The vaginal mucosa is succulent, and the vaginal walls are more rugous than is normally found in a girl of her age. The vaginal cytosmear contains masses of cornified cells. Hormonal assays may help in the diagnosis of granulosa cell tumors associated with greatly increased estrogen titers.

Deductions relating to the thyro-ovarian relationship are largely based upon the empirical observation that thyroid given as treatment in ovarian dysfunctional states frequently has a salutary effect. The basal metabolic rate, blood cholesterol determination and protein-bound iodine determination direct attention to thyroid dysfunctions and help in differentiating them from other causes of dysfunctional flow.

Nutritional, Constitutional and Psychic Factors. The diagnosis of nutritional, constitutional and psychic factors depends upon a careful general history, a complete examination and selected laboratory work. A dietary history and dietary studies are essential in nutritional problems. An evaluation of the state of the patient's blood not only gives the information relative to the amount of anemia caused by blood loss, but also may reveal unsuspected hematogenic causes for the flow. Psychic and emotional stresses severe enough to cause bleeding can usually be uncovered by the physician if he will take the time to seek out the situation which is the basis for the patient's problem.

Organic Disease of the Genitalia. Organic disease of the genitalia as a cause of uterine bleeding is unusual in the first half of the second decade. Follicular cysts and theca granulosa cell tumors characteristically cause an increased amount and irregularity of flow. Their presence is suspected when the adolescent girl evidences signs of increased estrogen stimulation. There is usually a marked increase in cornified vaginal cells seen in the vaginal cytosmear when estrogen-producing tumors are

present. Malignant tumors of the genitalia may cause continuous rather than intermittent or profuse bleeding. The flow which accompanies them may be mistaken for menstrual disturbances. The diagnosis of both benign and malignant neoplasms of the genitalia depends upon a thorough examination of the pelvis, often under general anesthesia.

Examination includes inspection of the vulva, visualization of the vaginal mucosa and cervix, vaginal and recto-abdominal palpation, vaginal cytosmears, and biopsy of unusual or suspicious lesions of the vulva, vagina or cervix. In exceptional cases peritoneoscopy, pneumoperitoneum roentgenography, curettage and abdominal exploration may be required.

The role of retrodisplacements of the uterus in the causation of abnormal uterine bleeding merits mention only to emphasize that congenital displacements are rarely factors in dysfunctional bleeding.

Although rare in adolescence, bleeding may be due to a complication of pregnancy. The diagnosis may seem obvious; however, it cannot be made with certainty without establishing the presence of fetal tissue.

Increase in Circulating Heparinoid Substances. Other causes for abnormal flow having been excluded, an evaluation of heparinoid substances is an essential part of the study of all cases of dysfunctional bleeding. The diagnosis of increased heparinoid substances depends upon identifying them in the circulating blood by a protamine titration. When the test is positive, it indicates that there is an excessive amount of circulating heparinoid substances in the patient's blood. The relationship between such substances and abnormal flow is borne out by the fact that the administration of toluidine blue to adolescent girls who suffer from dysfunctional bleeding associated with increased heparinoid substances is followed by a normal flow.

CONCLUSIONS

Amenorrhea, dysmenorrhea or profuse or prolonged menstrual flow stem from one of several causative factors. These problems are approached with the realization that the activation of the reproductive functions which characterizes the developmental period between childhood and maturity is a complicated process. Many of the factors which initiate, regulate or disturb it are unknown. Racial, familial and constitutional variants influence it through altering the rapidity with which the subject reaches sexual maturity. The diagnosis of menstrual problems in adolescence is made by differentiating among endocrine disturbances, abnormal nutritional states, systemic disorders, psychic problems, congenital defects or organic disease of the genitalia, all of which may be implicated as causative factors.

REFERENCES

1. Allen, J. G., et al.: A Protamine Titration as an Indication of a Clotting Defect in Certain Hemorrhagic States. J. Lab. & Clin. Med., *34*:473, 1949.
2. Dameshek, W., and Rheingold, J. J.: Idiopathic Thrombocytopenic Purpura and Menorrhagia Mistakenly Treated for Local Disease. J.A.M.A., *139*:993, 1949.
3. Dodds, E. C., and Robertson, J. D.: Masked Hypothyroidism as Cause of Amenorrhoea. J. Obst. & Gynaec. Brit. Emp., *46*:213, 1939.
4. Doyle, J. C.: Imperforate Hymen with and without Hematocolpos. J.A.M.A., *136*: 861, 1948.
5. Elghammer, R. M., et al.: Observations on the Clotting Mechanism in Menstruation and Menorrhagia. Surg., Gynec. & Obst., *89*:764, 1949.
6. Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood. Am. J. Dis. Child., *59*:579, 1940.
7. Hinman, F., Jr.: Sexual Trends in Female Pseudohermaphrodism. J. Clin. Endocrinol., *11*:477, 1951.
8. Hurxthal, L. M.: Hypogenitalism during the Usual Time of Puberty. J.A.M.A., *136*:12, 1948.
9. Jailer, J. W.: Diagnostic Significance of 17-Ketosteroids. M. Clin. North America, *36*:757, 1952.
10. Jarcho, J.: Malformations of the Uterus: Review of the Subject, Including Embryology, Comparative Anatomy, Diagnosis and Report of Cases. Am. J. Surg., *71*: 106, 1946.
11. Jones, G. S., and Smith, F.: Treatment of the Dysmenorrhea Symptom Complex; A Preliminary Report on the Uterine Relaxing Factor. Am. J. Obst. & Gynec., *67*:628, 1954.
12. Kinsell, L., Bryant, D., and Albright, F.: Rate of Growth of Axillary Hair as a Diagnostic Index. J. Clin. Endocrinol., *14*:897, 1954.
13. Larsen, M. S.: The Menstrual Cycle Length and Variability of Young Adult Women. Am. J. Obst. & Gynec., *54*:1069, 1947.
14. Menninger, K. A.: Emotional Factors in Organic Gynecological Conditions. Bull. Menninger Clin., *7*:47, 1943.
15. Mitchell, G. W., Jr., and Rogers, J.: The Influence of Weight Reduction in Amenorrhea in Obese Women. New England J. Med., *219*:835, 1953.
16. Montagu, M. F. A.: Adolescent Sterility. Springfield, Ill., Charles C Thomas, 1946.
17. Morse, A. H.: Carcinoma of Female Genital Tract in Childhood. Am. J. Obst. & Gynec., *19*:520, 1930.
18. Papanicolaou, G. N.: The Sexual Cycle of the Human Female as Revealed by Vaginal Smears. Am. J. Anat., *52*(Supp.):519, 1933.
19. Pollack, R. S., and Taylor, H. C., Jr.: Carcinoma of the Cervix during the First Two Decades of Life. Am. J. Obst. & Gynec., *53*:135, 1947.
20. Reynolds, E. L., and Wines, J. V.: Individual Differences in Physical Changes Associated with Adolescence in Girls. Am. J. Dis. Child., *75*:329, 1948.
21. Siegler, S. L., and Siegler, A. M.: Evaluation of the Basal Body Temperature (an Analysis of 1012 Basal Body Temperature Recordings). Fertil. & Steril., *2*:287, 1951.
22. Stein, I. F., and Leventhal, M. L.: Amenorrhea Associated with Bilateral Polycystic Ovaries. Am. J. Obst. & Gynec., *29*:181, 1935.
23. Theobold, G. W.: Centre or Centres in Hypothalamus Controlling Menstruation, Ovulation, Pregnancy and Parturition. Brit. M.J., *1*:1038, 1936.
24. Turner, H. H.: Syndrome of Infantilism, Congenital Webbed Neck and Cubitus Valgus. Endocrinology, *23*:566, 1938.
25. Whittaker, S. R. F., and Whitehead, T. P.: Diagnosis and Treatment of Hypopituitarism. Brit. M.J., *2*:265, 1954.
26. Wilkins, L.: Abnormalities and Variations in Sexual Development during Childhood and Adolescence. Advances in Pediatrics. New York, Interscience Publishers, 1948, Vol. III.
27. Wilkins, L.: Genetic and Endocrine Factors in the Growth and Development of

Childhood and Adolescence. Recent Progress in Hormone Research. New York, Academic Press, 1948, Vol. II.
28. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Springfield, Ill., Charles C Thomas, 1950.
29. Wilkins, L., et al.: Treatment of Congenital Adrenal Hyperplasia with Cortisone. J. Clin. Endocrinol., *11*:1, 1951.

670 North Michigan Avenue
Chicago 11, Illinois

THE FAT CHILD

MATTHEW M. STEINER, M.D.

Considering the frequency of fat children who are otherwise normal, one can assume that obesity in childhood is usually not an endocrine problem; it is not the result of hormonal disturbances, but is the expression of an imbalance between the intake of food and the output of energy. Though it has been suggested that alterations of the pituitary,[17, 18] thyroid,[11] adrenal,[13, 14] hypothalamus[8, 12] and pancreas[2, 31] may be contributing factors in the development of obesity, such instances in childhood are rare indeed. In fact, the fat child as a rule has no associated clinical endocrinopathy or intracranial disease. It is of historical interest that in 1930 Newburg[15] studied the total heat eliminated by the body and concluded that the energy exchange in all obesity, whether or not associated with other endocrine anomalies, followed the same general laws of energy. In other words, the child who eats and assimilates more food than he needs will gain weight; conversely, regardless of the cause of the obesity, loss of weight will result if the caloric intake is less than the expenditure of energy.

A child is said to be "fat" if the weight is 20 to 40 per cent above the normal. What, then, is considered the "normal"? If certain standards are used for judging the weight of the child—for example, the Baldwin-Wood height-weight tables[1]—there are many children with significantly large skeletal and muscular bodies who, though they do not appear clinically obese, may still fall into the 20 to 40 per cent above normal for this set of tables. Other standards, however, take into consideration the weight of the child in relation to the body structure and thus provide for the short child with soft tissues as well as for the one with a large bony and muscular framework. Such tables as the Pryor width-weight tables,[16] the Wetzel grid[4, 28–30] and the Stuart percentile tables[7, 22, 23] have been found more useful in the diagnosis and management of fat

From the Department of Endocrinology, Children's Memorial Hospital, Chicago.

children. The Wetzel grid, in addition, has served as an excellent illustration of the trend to obesity as it developed and the progress of weight reduction; both patients and parents have been impressed favorably with such a graphic picture during the management.

ETIOLOGIC FACTORS

The factors responsible for the excessive intake of food are protean in origin and nature. In a large group of children a decided increase in weight occurs close to puberty and is part of the spurt in growth and development of bone and muscle. Most of these children are happy and well adjusted, and the fat "thins out" as the growth spurt continues. It would seem unnecessary to make an issue of such self-limited types of overweight, and certainly to administer anorexigenic medication to such adolescents. Some children at this age have minor emotional difficulties and embark on various eating jags or nibbling between meals, after school or at bedtime. Such minor disturbances can usually be soothed by the sympathetic parent or the understanding physician, and the overeating will correct itself when the emotional turmoil subsides.

CASE I. E.G., a 12 year old white boy, had gained 10 pounds in about 3 months. Previously he was well adjusted, happy and a good student. Some months prior his family had moved to another city, and he found it difficult to make new friends and adjust to the new school. The parents reported that, while he had a good appetite and usually ate only at mealtimes, he now nibbled between meals and consumed a lot of food at bedtime. Also, he watched television during every spare moment, at which time he would eat constantly. On examination there were no unusual physical findings other than the obesity. He admitted that he was unhappy, missed his boy friends and gymnasium group, and found it hard to keep up with his school work. After consultations with the parents, a tutor was obtained to help with the schoolwork, he was enrolled in a Scout group, and he joined the local "Y" for swimming and athletics. Without medication or prescribed diet he reduced his excessive eating and gradually lost weight (Fig. 23).

The fat child in whom we are particularly interested is the one who shows excessive and progressive gain in weight long before the changes of adolescence, or one in whom such marked increase in weight occurs at times of emotional crises during or after adolescence and continues for some time afterwards. Such children differ markedly from the aforementioned group in that they are consistently unhappy and poorly adjusted at home and at school; they feel insecure both with their elders and with their own age group. To such children, eating assumes a totally different meaning from what it does to most of us. It is not only a means of appeasing hunger in itself—it is often the only means of satisfaction they obtain from their own environment. Food then becomes a weapon against "stress and strain" and at times the only source of comfort.[5, 9] Since such children lack the ability to get enjoyment from the normal experiences about them, and they use food excessively as a substitute

for such enjoyment, no attempt to withhold food or curb the appetite will solve the problem or correct the obesity. Furthermore, the necessity for overeating is aggravated by the tendency of such children to exclude themselves from normal social activities of the group and thus fail to develop interest and social skills vital for the full development of their

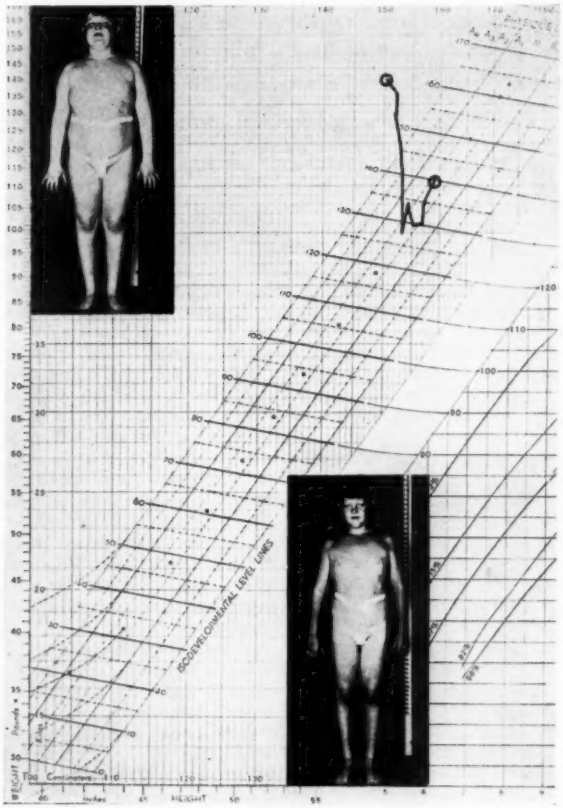


Fig. 23.

personalities. Many use their obesity further as an excuse for refusing to take part in social and athletic activities; thus a vicious cycle is set up which can be broken, not by threatening to withhold food, but only by a sympathetic understanding of the problem and the substitution of other gratifications more normal than that obtained so easily by overeating.

The child who needs more than casual dietary supervision is the one who shows emotional and personality disturbances when overeating is

the expression of such difficulties. To attempt the management of such obesity with diet alone or with one of the appetite-suppressing medications, without an appreciation of the basic disturbance in the child, is to invite resistance and ultimate failure of any therapy. In the beginning, even such children may do well with a weight reduction regimen; the novelty of the procedure and the added attention from parent and physician may produce some transient effect, but in the long run these children resist withholding of food and eventually require much help in solving their emotional and social problems.

Case II. R.V., a 4 year old white girl, weighed 76.5 pounds and was 44 inches tall. According to several standards she was between 25 and 30 pounds overweight. She was an unhappy, poorly adjusted child and did not play with other children. Not only would she eat between meals, but she had been awakening during the night and would eat whatever left-overs she could find in the pantry or refrigerator. Aside from marked obesity there were no other unusual physical findings (Fig. 24, left, upper group). The father and mother had separated soon after this child had been born. The mother was employed in a factory, and the care of the child was left to grandparents, friends and occasional hired domestics. She had been overprotected and was not permitted to play on the street with other children. She had been mistreated and punished by many who took care of her while the mother was at work. In view of the circumstances, a day nursery was recommended, and the child responded well to the opportunity of being with other children her own age for the first time. A 1200-calorie diet was prescribed together with 5 mg. of Dexedrine Sulfate three times daily. The left lower grid illustrates the loss of weight in 11 months (15 pounds). The photograph in the upper group, right, shows this child at the end of this period of management. She was happy, enjoyed being with other children and appeared better adjusted to the idea that her mother had to be away from her all day at work.

World War II interrupted the observation in this case. She was again seen in October, 1946 (Fig. 24, lower group, left). She weighed 146½ pounds and was 53 inches tall at age 9½ years. She was sullen and morose and refused to speak when questioned. In the interim between 1942 and 1946 the mother had remarried an Army man, with whom she moved from camp to camp as orders changed. He was sent overseas and was killed in battle. Again various group activities were suggested as a vital adjunct to the management of this child's problem. An interested Girl Scout leader developed many new interests in this child, and she was again given the above prescribed diet and medication. She began to excel in swimming and camp craft and soon re-educated her eating habits so that medication was discontinued. In 14 months her weight dropped to 111 pounds (Fig. 24, lower group, right).

In January, 1948, the mother remarried, and the family moved again. Girl Scouts and friends were gone again. The child refused to eat the prescribed food despite increasing amounts of Dexedrine Sulfate. Within the year she had gained 10 pounds. The family moved to another city, and she could no longer be observed.

Hence the primary factors responsible for the imbalance between the intake of food and the output of energy in the majority of such obese children can be attributed to the social and emotional problems of the child. The obesity, then, is an expression of a basic disturbance in the harmonious development of the personality of the child. In short, it is not only the obesity which requires our attention, but also the problem of the child as a whole and the part this plays in the initiation and persistence of that obesity.

CLINICAL FEATURES

The clinical approach to the fat child differs in many respects from that of the usual patient. The physician would be well rewarded in devoting time and effort not only to the child, but also to the parents. In

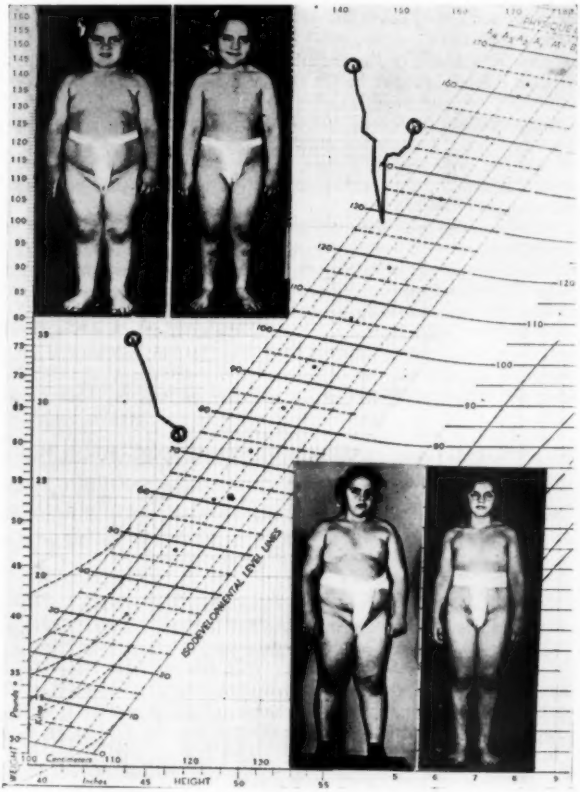


Fig. 24.

many situations he must overcome the common attitude that "there is something wrong with the glands" and pave the way to a better insight into the underlying factors responsible for the obesity. Consultations with the parents can yield valuable information concerning the effects of home environment and afford a method of constructing a growing-up picture of the child.

The following questions are not meant to be exhaustive, but have been useful as a basis for the investigation and have produced many

facts helpful to a better appreciation of parent-child relationship and attitudes of the child to the environment.

1. What is the attitude of the parents to one another?
2. Has there been a separation or remarriage?
3. Who is the disciplinarian in the family?
4. What part does the father assume in family guidance?
5. What is the social and economic position of the family in relation to food and the care of the patient?
6. What was the attitude of the parents to the birth of the child?
7. Was there disappointment in the sex of the child, and is there evidence of rejection?
8. How many children are there in the family? Where does the patient stand in the group? Is there preference for any one child?
9. What was the early feeding history and type of feeding schedule?
10. What was the early infant welfare in relation to food—such as colic, diarrhea, vomiting and changes of formula?
11. What was the attitude of the mother to food and the possible use of food as an emotional outlet?
12. What was the attitude of the mother to the child—affection and overprotection, awareness of the needs of the child for love and security?
13. What was the attitude of the parents to the process of growing up? Was the child encouraged to become self-reliant, competent and creative? When did the child begin to dress, cross streets, run errands, accept home responsibilities and visit friends?
14. How much discipline and corporal punishment, and for what reason?
15. What is the approximate diet of the child at home, and what food is eaten in excess?

Likewise, informal talks with the patient apart from the routine physical examinations will enable the physician to gain an insight into the problem from the viewpoint of the child and thereby develop some satisfactory outlets which can serve as a motivation for cooperation with the entire program.

1. Does the child want to lose weight? In some families, parents are more anxious about the weight of the child, while in others it is the child who initiates the effort for weight reduction. Whether the desire to lose weight is based on "wishing to play better ball," "wear pretty dresses" or because "they call me fatty," the answer to the main question often gives the clue to the development of some motivation for adherence to the program. Here also one may gain some impression about the feelings of the child to its social environment and how the obesity may be used as an excuse from taking part in various activities.
2. What are the school experiences, activities and grades?
3. What are the activities after school hours?
4. Membership in social groups, gymnasium and Scouts.
5. What are the attitudes of the child to the parents—affection, respect, tolerance and discipline?
6. Nature of leisure time, family outings and vacations.
7. Does the child confide in either parent, or does he seek outside friends or relatives?
8. Does the child have too many responsibilities at home? Is he "tied down" to a younger brother or sister?
9. What are the attitudes of the parents to the excessive intake of food, discipline at the table, use of food as a weapon or bribe?

Regular consultations should be held with both parents and patient, and the management should be individualized according to the findings

in each family unit. Thus a working basis may be developed not only for the solution of the child's problems, but also for the guidance of the parents. At certain intervals, and for the purpose of stressing a general approach to the basic derangement in obesity, older children can be brought together as a group; the sharing of individual experiences in management has proved helpful in some groups of patients.

The fat child is often alert, cooperative and has good school grades. There are no stigmata of endocrine or intracranial disturbances. The height is normal or above normal as judged by height-age tables. The adipose tissue may be generalized or concentrated about the breasts, abdomen or hips. In boys the suprapubic fat may be so extensive and pendulous as to give the impression that there is hypogonadism.

CASE III. M.C., a 10 year old white boy, was referred to us because of hypogonadism and "Froelich's syndrome." He was an alert boy, well adjusted, and did well at school. He was popular at school and spent a good deal of his time after school at the drug store with his friends. There was a history of excessive intake of snack foods and soft drinks. There was no evidence of intracranial disease. The adipose tissue was concentrated about the abdomen and hips, and there was an apron of fat in the suprapubic area (Fig. 25, upper left). With retraction of the suprapubic fat, the penis was of average size and the testes were normal. After a short-term low calorie regimen the loss of weight was sufficient to disclose normal-appearing external genitalia (Fig. 25, lower right).

Young girls may appear to have fully developed breasts. Pinkish-white striae may be present over the stretched skin of the abdomen and hips in contrast to the purplish striae in some cases of Cushing's syndrome. Some fat children have flabby tissues, while others, particularly around puberty, may have well developed musculature with large skeletal frames. The eyegrounds, visual fields and extraocular movements are normal. The head, neck and chest are not unusual. The blood pressure may be elevated moderately, and it is well to remember that the use of a small pediatric cuff on a large obese arm may result in some overestimation of values. Though the extremities are usually normal, some fat children complain of vague aches and may have varying degrees of flat feet. The genitalia are normal.

Roentgenograms of the skull (sella) are normal. Skeletal maturation is either normal or moderately advanced for the chronologic age.[26] The basal metabolic rate varies considerably with the use of different reference standards, for we are dealing with obese children having abnormal body proportions;[3, 10, 19, 21, 24, 25, 27] the errors may be so large that the determination of the basal metabolic rate serves no purpose in the final evaluation of the obese patient. The values of serum cholesterol are not significant. There is also no correlation between the basal metabolic rate, the serum cholesterol and skeletal maturation.[6] Our recent studies with radioactive iodine have indicated that the obese child has a normal uptake (euthyroid). Hence we have not used thyroid medication in the

management of obesity in children. In general, the routine examination of the fat child reveals an alert patient of good stature with varying degrees and distribution of adipose tissue, with no localizing endocrine or neurologic findings, in whom laboratory investigations are not contributory.

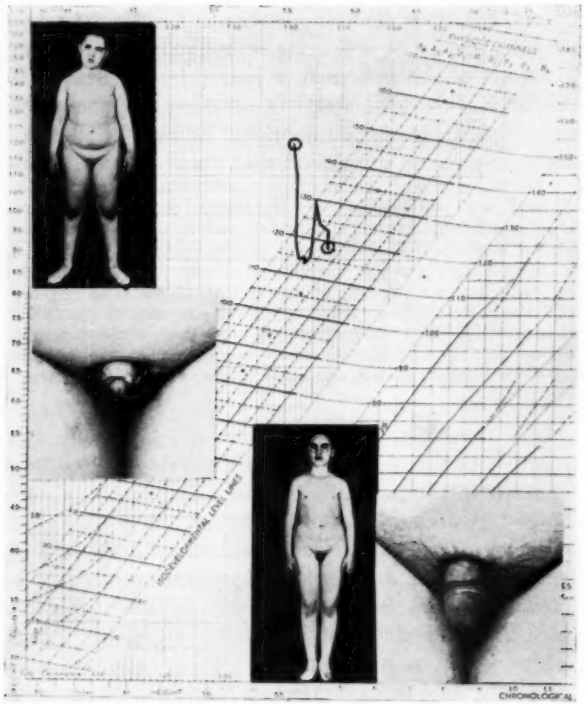


Fig. 25.

MANAGEMENT

There is no favorite formula or short-cut in the management of obesity in childhood.[20] Low calorie diets and appetite-suppressing medication are only minor aids for such children. It is well to remember that each child brings to the physician not only his own problems, but also those of the family, the school and the environment. It is far more essential to understand the basic disturbance in the child than to insist upon strict adherence to a dietary regimen which, in itself, may increase the insecurity of the child and bring about resistance to the whole program.

The actual criteria for the management of the fat child depend upon the findings in each family unit. It is often necessary to stress the role of the father in more direct and positive participation in family guidance. In the face of maternal difficulties, other outlets are devised for the mother so that overfeeding and overprotection will not hamper the child's drive for independence and self-reliance. If the obese child is old enough to understand the basis for overeating, he is encouraged to realize the necessity for cooperating in activities and group interests. It is not a simple matter to develop an interest in an environment which the child fears; the parents are encouraged to be gentle and patient. For the preschool child, nursery groups are helpful. For the older ones, social or teen-age groups, "Y" groups and Scouts often prove valuable adjuncts in the over-all adjustment and management.

Diet

The diets are composed of low fat, moderate carbohydrate and high protein with adequate amounts of calcium and daily vitamin supplement. There are no hard and fast rules for choosing one of three basic diets: 1000-, 1200- and 1500-calorie diets. In general, for the younger or markedly obese patient, the 1000-calorie diet is suggested, and additions are made as desired. The essential purpose of a dietary regimen is to re-educate the eating habits of the child while social and environmental adjustments are attempted. Some fat children need little or no dietary management and may lose weight simply by absorbing new interests and satisfactions while family problems are being solved. This is also true for some adolescents with minor emotional crises. Others, however, require a "strict" dietary program with appetite-suppressing medication, especially at the onset of treatment. This includes a large group with complicated family situations, inadequate adjustments to school and social affairs, and those in whom it is difficult to stimulate the acquisition of new interests. As the weight decreases to about 10 per cent above the estimated weight loss, the calories are increased. In some adolescents a spurt in growth may develop so that the intake is increased above 1500 calories in order to prevent the child from appearing actually too thin!

To make a 1200-calorie diet from the basic "1000," add 2 ounces of whole milk to each meal, ½ thin slice of bread (whole wheat) to the dinner and supper with 1 level teaspoonful of butter on each, and a serving of tomato juice at 3:30 P.M. To make a 1500-calorie diet from the basic "1000," add 1 thin slice of bread (whole wheat) and 1 level teaspoonful of butter to each meal, 2 ounces of milk to each meal and a serving of tomato juice at 3:30 P.M.

TABLE 20. *1000-Calorie Diet*

FOOD	AMOUNT
Breakfast:	
Fruit	1 serving (any allowed on list below)
Cereal or bread	½ cup cooked or 1 thin slice
Egg	1 cooked any way except fried
Milk (whole)	6 ounces
Dinner:	
Lean meat or substitute	1 small serving (1¾ oz.) (See list of meats)
Vegetable	1 cup (any allowed on list below)
Fruit	1 serving (any allowed on list below)
Milk (whole)	6 ounces
3:30 P.M.:	
Fruit	1 serving (any on allowed list)
Supper:	
Lean meat or substitute	1 small serving
Vegetable	1 cup
Fruit	1 serving
Milk (whole)	6 ounces

FRESH FRUITS ALLOWED

Apple	1 small
Apricots	3 medium
Blackberries	1 cup
Cantaloupe or honeydew	1 cup (1-inch cubes)
Cherries	½ cup
Grapefruit	½ medium size
Grapefruit juice	½ cup (unsweetened)
Orange	1 medium
Orange juice	⅓ cup
Peach	1 medium
Pear	1 small
Pineapple	⅔ cup diced
Pineapple juice	⅓ cup (unsweetened)
Plums	3 medium
Raspberries	1 cup
Strawberries	1 cup

FRESH OR CANNED VEGETABLES ALLOWED

Asparagus	Cucumbers	Radishes
Beets	Endive	Rutabagas
Beet greens	Kale	Sauerkraut
Broccoli	Kohlrabi	Spinach
Cabbage	Lettuce	String or wax beans
Carrots	Mustard greens	Squash
Cauliflower	Okra	Swiss chard
Celery	Onions	Tomatoes
Celery cabbage	Peppers	Turnips
Collards	Peas	Turnip greens

General Information on Low Caloric Diets

Meat or Meat Substitute:
Lean meat means any meat, with the fat trimmed off, chicken and fish.
One small serving equals one small chop or ¼ cup of ground meat.
Cottage cheese may be used in place of meat—1 serving equals ¼ cup.
American cheese may be used—1 serving equals 1 thin slice (loaf).
Bacon, salt pork and sausage are fat meats and may not be used.

Soup:
Broth may be used if desired if all the fat has been removed.
Vegetables on the allowed list may be added to this broth.

Cereals:
Dry cereals may be used in place of the cooked cereals—1 serving equals ⅔ cup.

Salt:
No additional salt should be used, and only a small amount in cooking.

General Rules

1. Do not use sugar, honey, jam, jelly or candy.
2. Do not use fruits canned with sugar.
3. Do not use cake, cookies, pie, puddings, ice cream or ices.
4. Do not use foods which have cornstarch or flour added such as gravy or cream sauce.
5. Do not use potatoes (sweet or Irish), macaroni, spaghetti, noodles, dried beans or peas.
6. Do not use fried foods prepared with butter, lard, oil or butter substitutes.
7. Do not use drinks such as Coca-Cola, ginger ale, pop or root beer.
8. Do not use any foods not allowed on the diet, and only the amounts specified in the list.

Drugs

Anorexigenic drugs[32] have a place in the medical management of the fat child. The sense of well-being and suppression of appetite which such medication produces in many instances bring about a fairly effortless loss of weight; such an effect is excellent for the morale of the patient early in the management. However, it cannot be relied upon to take the place of understanding and solution of the underlying problems of the child and the family. Children seem to tolerate such medication better than adults, and there has been little toxicity even with continuance over many months. Except for a few instances of abdominal pain, headache and restlessness at night, most children have been able to tolerate doses of 5 mg. three times daily—before breakfast, before lunch and about 4 P.M. (Benzedrine or Dexedrine Sulfate).

There are many types of medications on the market at present, and mention will be made only of those which the author has used. Racemic amphetamine sulfate (Benzedrine Sulfate—Smith, Kline and French) was one of the earliest medications used in this type of therapy. It comes in 5- and 10-mg. tablets, and either strength may be used, depending on the age and size of the patient. Recently, Benzedrine Sulfate Spansule (15 mg.) has been introduced; this capsule contains wax-coated granules designed to prolong the action of the drug; it can be given before breakfast once daily. D-amphetamine sulfate (Dexedrine Sul-

fate—Smith, Kline and French) comes in 5-mg. tablets, and the Spansule in 10- and 15-mg. strengths. We have used the Dexedrine tablet or Spansule more frequently because of the greater tolerance in the younger patient. Usually, the 10-mg. Spansule has been found adequate once before breakfast. Some of the older adolescents have been hungry with even the 15-mg. Spansule before breakfast; we have either given the Spansule before lunch or added one 5-mg. tablet of Dexamyl before supper (Smith, Kline and French—containing 5 mg. of Dexedrine and 0.5 mg. of Amobarbital). For those who have complained of being "jumpy" or restless on Dexedrine Spansule, we have used Dexamyl Spansule (Spansule #1 contains 10 mg. of Dexedrine and 1 mg. of Amobarbital. Spansule #2 contains 15 mg. of Dexedrine and 1.5 mg. of Amobarbital). Obocell (d-amphetamine phosphate, 5 mg., and methylcellulose, 2½ grains—I. Neissler & Co.) can be used intermittently with other medications three times daily as indicated above. The "fullness" resulting from the swelling action of methylcellulose may be a factor in the success of this type of medication. It must be constantly realized that such therapy is temporary and cannot be relied upon to maintain the patient for any length of time.

Though there is no question concerning the benefit of anorexigenic medications in the treatment of the fat child, it must not be overlooked that unless the child's problems are solved, neither diet nor medication will bring about a satisfactory loss of weight. These problems must be solved if the child is to re-educate his eating habits, partake in greater activity and develop greater self-esteem to cope with his environment.

REFERENCES

1. Baldwin, B. T., and Wood, T. W.: Weight-Height Age Tables. New York, American Child Health Association, 1920.
2. Barnes, B. O., and Keeton, R. W.: Experimental Obesity. Am. J. Physiol., 129: 305, 1940.
3. Bruch, H.: Obesity in Children. Am. J. Dis. Child., 58:1001, 1939.
4. Bruch, H.: Grid for Evaluating Physical Fitness. J.A.M.A., *118*:1289, 1942.
5. Bruch, H.: Psychological Aspects of Obesity. Bull. New York Acad. Med., 24:73, 1948.
6. Bruger, M., and Poindexter, C. A.: Relation of the Plasma Cholesterol to Obesity and Some of the Complicating Degenerative Diseases. Arch. Int. Med., 53: 423, 1934.
7. Burgess, M. A.: Construction of Two Height Charts. J. Am. Statist. A., 32:290, 1937.
8. Farber, J. E., Gustina, F. J., and Postoloff, A. V.: Cushing's Syndrome in Children. Am. J. Dis. Child., 65:593, 1943.
9. Freed, S. C.: Psychic Factors in the Development and Treatment of Obesity. J.A.M.A., 133:369, 1947.
10. Lewis, R. C., Kinsman, G. M., and Ileff, A.: Basal Metabolism of Normal Girls and Boys from 2 to 12 Years. Am. J. Dis. Child., 53:348, 1937.
11. MacKay, E. M., and Sherril, J. W.: Influence of Thyroidectomy on Fat Deposition in Rat. Endocrinology, 25:518, 1941.

12. Marks, T. M., Thomas, J. M., and Warkany, J.: Adrenocortical Obesity in Children. Am. J. Dis. Child., 60:923, 1940.
13. Newburgh, L. H.: Obesity. Arch. Int. Med., 70:1033, 1942.
14. Newburgh, L. H.: Obesity. Physiol. Rev., 24:18, 1944.
15. Newburgh, L. H., and Johnston, M. W.: Determination of Total Heat Eliminated by the Human Body. J. Clin. Investigation, 8:147, 1930.
16. Pryor, H. B.: Width-Weight Tables. 2d ed. Stanford, Stanford University Press, 1940.
17. Reiss, M.: Lactogenic Hormones and Fat Metabolism. Endocrinology, 40:294, 1947.
18. Rowntree, L. G., and Brunsting, L. A.: Water or Fat? Water Retention in So-Called Endocrine Obesity. Endocrinology, 17:377, 1933.
19. Short, J. J., and Johnson, H. I.: Increased Metabolism in Obesity. J.A.M.A., 106: 1776, 1936.
20. Steiner, M. M.: The Management of Obesity in Childhood. M. Clin. North America, 34:223, 1950.
21. Strong, J. M., and Evans, F. A.: Energy Exchange in Obesity. J. Clin. Investigation, 6:277, 1928.
22. Stuart, H. C.: The Children's Medical Center, Boston—Anthropometric Chart. Boston, Harvard School of Public Health.
23. Stuart, H. C., and Meredith, H. V.: Use of Body Measurements in the School Health Program. Am. J. Pub. Health, 36:1365, 1946.
24. Talbot, N. B.: Basal Metabolism Standards for Children. Am. J. Dis. Child., 55:455, 1938.
25. Talbot, N. B., Worcester, J., and Stewart, A.: New Creatinine Standards for Basal Metabolism and Its Clinical Application. Am. J. Dis. Child., 58:506, 1939.
26. Todd, T. W.: Atlas of Skeletal Maturation. St. Louis, C. V. Mosby Company, 1937.
27. Topper, A., and Mulier, H.: Basal Metabolism of Children of Abnormal Body Weight. J.A.M.A., 92:1903, 1929.
28. Wetzel, N. C.: Physical Fitness in Terms of Physique, Development and Basal Metabolism. J.A.M.A., 116:1187, 1941.
29. Wetzel, N. C.: Assessing the Physical Condition of Children. J. Pediat., 22:82, 1943.
30. Wetzel, N. C.: Grid for Evaluating Physical Fitness, Cleveland, NEA Service, Inc.
31. Whipple, H. O.: Present Day Surgery of Pancreas. New England J. Med., 226: 515, 1942.
32. Williams, R. H., Daughaday, W. H., Rogers, W. F., Jr., Asper, S. P., Jr., and Towery, B. T.: Obesity and Its Treatment, with Particular Reference to the Use of Anorexigenic Compounds. Ann. Int. Med., 29:510, 1948.

6354 North Broadway
Chicago 40, Illinois

THE THIN CHILD

JOSEPH A. JOHNSTON, M.D.

In a random sampling of 1000 chief complaints among private patients, concern over a child's being "underweight" or "undernourished" proved, somewhat to our surprise, only slightly more frequent than that of obesity. This probably reflects the economic strata from which the patients derived and might not be expected to be true in a cross section of patients from an indigent group. When the complaint seemed justified by clinical assessment—and this was true in only half the cases—it was least often due to the availability of a good diet, but rather reflected a disease process which resulted in either anorexia or impaired utilization of the intake.

The two main problems confronting the pediatrician in these situations are (1) the method of assessment and (2) the extent to which weight can be taken to reflect adequate nutrition.

ASSESSMENT OF FAILURE OF WEIGHT GAIN

Throughout the literature there appear numerous attempts to supplement the information obtained from height and weight with other items that would qualify the inferences drawn from them—arm girth, pelvic width, chest circumference, bone age and many others. It has seemed to us that none of these added appreciably to the information obtained from the rough classification obtained on a first appraisal with the Wetzel grid, or graphs utilizing a percentile ranking. Departures from the mean referable to endomorphy or ectomorphy would still be included in the channels that described the highest and the lowest percentiles, or fell three sigmas beyond the mean. The grid itself, however, becomes highly dependable only when it is possible to plot more than one observation and thus measure a growth process rather than record a single observation. It serves the useful purpose, however, of calling attention to a condition warranting further study. For an excellent

From the Department of Pediatrics, Henry Ford Hospital, Detroit.

critical discussion of the point, with particular reference to the Wetzel grid, see Krogman.[5]

More difficult is the problem of the extent to which the information gained from height, weight and age carries with it inferences on nutrition implying some knowledge of the composition or quality of tissue. There are no over-all measurements that describe this. Such fragmentary knowledge as we possess that would relate nutrition to the occurrence of and resistance to infection relates chiefly to protein metabolism, and we have been able to show for periods as long as six months discrepancies between the storage of nitrogen and calcium and the gain in weight. In our studies of tuberculous adolescents, weight might be gained during nitrogen losses; conversely, a child would replenish depleted nitrogen stores while losing weight, apparently fat and water. Over longer periods the two will tend to parallel each other, and predictable amounts of nitrogen will constitute fixed proportions of weight. Marked deficits will fail to be reflected in measurements of the serum proteins, and the only practicable method we have of determining composition is by the cumbersome technique of balance studies. Since this approach is obviously impossible as a clinical procedure, we are left for the time being only with the inferences that can be drawn from a good history of dietary intake, and a careful appraisal of all those factors which influence the storage of this vital item. Numerous examples of the discordance between the two measurements are recorded elsewhere.[2]

In Infancy

The clinician's approach to the problem of "gaining at too slow a rate" or being "too thin" will be quite different in the periods of infancy and childhood. Though this paper has to do largely with the latter, a few comments will supplement the excellent discussion of the problem in infancy given by McCune.[6] In the infant, the framework of our thinking will take this form:

1. Congenital defects of major systems:
   Cardiovascular
   Genitourinary
   Gastrointestinal
   Central nervous
   Osseous
2. Adequacy of the dietary intake
3. Utilization of the dietary intake, as inferred from stools or appropriate tests when indicated (oral glucose tolerance, fat absorption)
4. Infection
5. Allergy
6. Environment—the attitudes of parents and siblings
7. Thyroid disturbances

Congenital Defects. It has been fairly common in our experience to have to give a mother her first information that her child had a congenital heart defect when the presenting complaint had to do only with failure to gain. Incidentally, it has been possible frequently to improve this situation by a modification of the feeding schedule to provide smaller volumes of more concentrated mixtures at more frequent intervals.

Congenital defects in the urinary tract have likewise been discovered when the explanation for failure to gain was not too obvious; and largely by exclusion, pyelography was resorted to.

In the gastrointestinal field it should be recalled that the history of the celiac will tell of failure to gain at the normal rate months in advance of the passage of stools that make the diagnosis obvious. It has been one of our arguments that this condition—granted a multiplicity of contributing etiologic factors—has in a considerable number of instances an underlying background of hypothyroidism on which is superimposed the trigger mechanism of infection, allergy and emotional factors.[3]

The difficulty in promoting gain in the cerebrospastic is well recognized. In this group, however, as in the congenital heart group, it is often possible to effect some degree of improvement in spasticity by satisfying his extra caloric needs with concentrated, high-caloric mixtures. Admitting that the spasticity has its origin in a nervous system defect or injury, an added increment can be contributed by poor nutrition and be comparable to that seen in the marantic state. I have seen at least a 30 per cent improvement in a severe spastic when weight gain was promoted by the feeding regimen suggested.

The Dietary Intake. It is an interesting commentary on current feeding practices that, in contrast to an analysis I made 30 years ago, when failure to gain in infancy could most often be attributed to mixtures inadequate in calories and repeatedly made more dilute because an infant's crying was interpreted as intolerance, today faulty mixtures would represent the least common cause for failure to gain. Probably the most common modification I have had to suggest has not involved any radical change in the composition of the formula, but the inclusion of a flour thickening for the infant with pylorospasm, and the use of an antispasmodic.

Infection. Low grade lymphoid infection evidenced by obstructive breathing and cervical adenopathy, usually of the posterior cervical group, is a common cause of failure to gain. When it persists long enough, we feel that it is in the background of a fair percentage of cases of chronic intestinal indigestion.

Allergy. Though the allergic state in general is not conducive to normal gain, the promiscuous withdrawal of items such as milk, egg and

meat on suspicion is not to be undertaken lightly. Occasionally, brilliant results may follow the substitution of a nonmilk source of protein, but meantime hyposensitization with minute amounts can be undertaken. We have seen too many infants and children kept poorly nourished by the removal from their diet of these items for indefinite periods of time. As Blackfan pointed out repeatedly, the normality of a child's nutritional state is far more important than his eczema.

Environment. I have admitted for observation infants in whom I could find no cause for failure to gain, only to have them do perfectly in the hands of a quiet, understanding nurse, but revert again to a state of irritability and failure to gain when returned to an apprehensive mother. "Nervous indigestion" can manifest itself in the first few months of life with inept handling.

Thyroid Disturbances. The infant with hypothyroidism of a degree less than overt cretinism presents a diagnostic problem. Lacking the help from facies and body configuration seen in the full-blown cretin after seven weeks, we have recourse, in the infant in whom the question has been raised, to laboratory aids. The bone age, cholesterol, alkaline phosphatase, protein-bound iodine and uptake studies have all, in our hands, had a sufficiently wide range to make them equivocal save in the instances in which the diagnosis was obvious enough to place them in a merely confirmatory role. Recourse to a therapeutic trial is justified when other causes for failure to gain have been excluded, and when these aids at least supplement the clinical impression. Sensitivity of response to small amounts will be a further diagnostic aid.

In Children

Turning now to the older child brought for failure in weight gain, the following outline of history and physical examination is suggested:

Inheritance. The potential for growth will obviously be influenced by this, but, as implied before, in the averaging process involved in percentile ranking or a frequency curve this item is covered. Unless, however, the information gained by plotting height against weight is supplemented by a note on progress of both these dimensions plotting against age, a false estimate can be made. There will be given in a later place an example of a child whose parents complained of slow growth for years before we appreciated the seriousness of the situation because her weight for height was not grossly abnormal and because her parents were small. Her plotting on the right-hand side of the grid was very revealing.

Age. Parents have constantly to be reminded that there are years in the growth process which can be thought of as "thinning" years, in

which the gain in weight per unit of height is much less than at other periods—notably the preschool years.

Dietary Intake. A brief note on the intake of meat, egg, fish and milk and a source of vitamin D will immediately dispose of the question of the adequacy of protein and calcium intake, and thereby permit inferences on the quality of tissue. A story of a high protein intake with a correspondingly lower intake of carbohydrate immediately reassures one in assessing the child whose weight places him in the questionable group. Particularly in the younger age group, however, this information is promptly to be supplemented by a story of the stools for the light this may throw on the question of the utilization of the intake.

Regimen of Living. A brief note on the day's activities from the time of arising to going to bed is in order. In an analysis of reasons for thinness in children from the better economic circumstance made for the 1930 White House Conference I felt I was able to explain the great majority by infection, but there was a group of fatigued, undernourished adolescents who stood out as a special problem. A strenuous school schedule commonly at the level of junior high school, with a hasty 20 minute lunch period, supplemented by extracurricular activities, social and athletic, not uncommonly added up to an expenditure of energy not balanced by an adequate intake of food or sufficient rest.

Infection. The most common cause for failure to gain in the presence of a seemingly adequate intake of food was chronic infection of the upper respiratory tract. The removal of chronically infected tonsils has long been known to be followed by a sharp gain in weight. Because it was desirable to know the composition of this newly gained tissue, we did nitrogen balances on nine children before and after removal of the infected tonsils. Nitrogen retention increased from 0.06 gm. per day to the normal figure of 1.52 gm. The storage of calcium in one case increased threefold. This is of interest in demonstrating an actual catabolic effect of a focus of infection not explained by fever.[1]

A variety of other processes appeared in the survey—rheumatic fever and tuberculosis among them. As stated earlier, a basis for failure in nutrition was assignable to some cause other than food in 96 per cent.

Thyroid Disturbances. Residence in a goiter belt probably colors our experience in this field. There is reproduced the grid of a boy brought in at eight because of slowing down in rate of gain and failing in third grade work. If we had not had previous measurements on him, we would not have been unduly concerned with his channel classification, but the fact that he had dropped down two channels led to a careful physical examination and a determination of basal metabolism. When this was found to be as low as —25 and thyroid was started, the effect on gain was striking. In the next 12 months he gained 22 pounds in weight and

4 inches in height, and incidentally improved beautifully in school work. It should be recalled that one measurable effect of thyroid when given to the hypothyroid is the increase in the span of attention, and that the effect on tissue is highly anabolic for both nitrogen and calcium. This effect is reversed, however, with doses that are too large or when thyroid is given to a normal person.

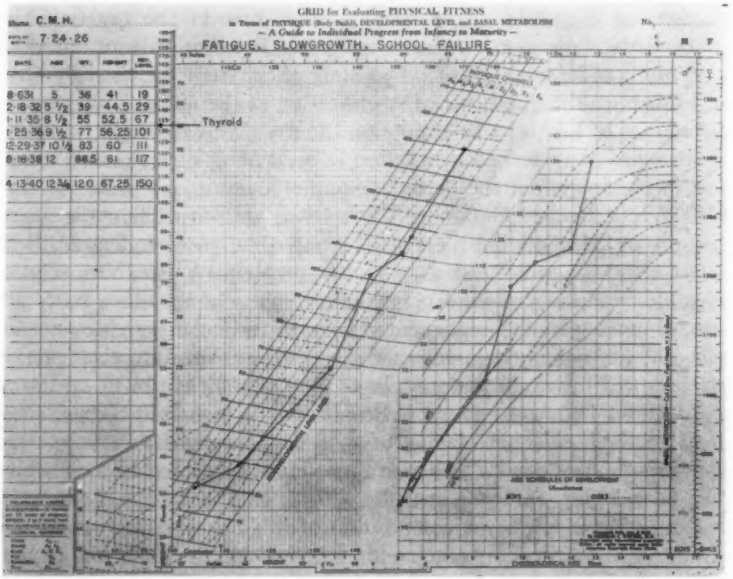

GRID for Evaluating PHYSICAL FITNESS
— A Guide to Individual Progress from Infancy to Maturity —
FATIGUE. SLOWGROWTH. SCHOOL FAILURE
Thyroid

Fig. 26. Growth failure referable to thyroid insufficiency. Note the drop from Channel B1 to B3 and the regaining of 34 developmental level points in the year after the use of thyroid.

An example of smallness and growth failure referable to the pituitary is included to bring out the point that we were less concerned about this child, whose parents were small, than we should have been because weight for height was not particularly out of line. The gain in both directions, however, plotted against time on the right-hand side of the Wetzel grid was striking. Evidences of increased pressure from the cyst were not evident until she was 12.

CONCLUSIONS

An assessment of the normality of weight is possible from a charting either of percentile ranking or a frequency curve. Inferences on the extent to which weight reflects the normality of nutrition can be made

from a good dietary history and a thorough survey that has in mind all those factors which influence growth—infectious, glandular and emotional. In the middle and upper economic strata the explanation for growth failure will least often be found to be faulty intake of food.

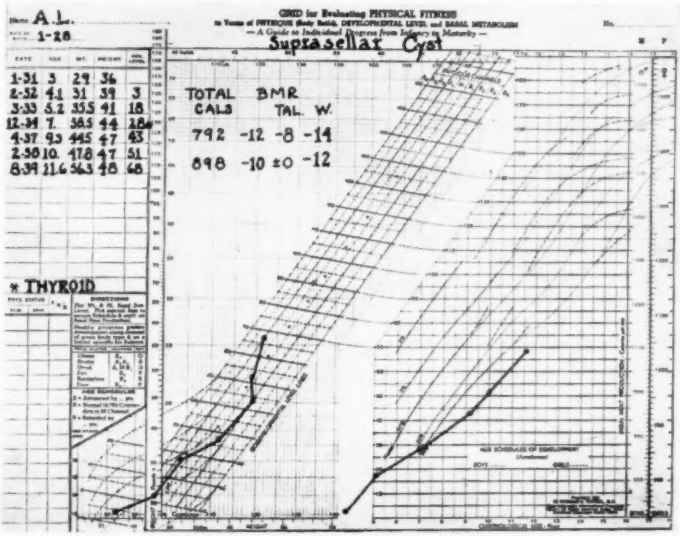


Fig. 27. Growth failure referable to pituitary deficiency. Note that weight for height in December, 1934, was not particularly revealing, nor even in 1937, but that progress on the auxodrome was grossly abnormal.

REFERENCES

1. Johnston, J. A.: Focal Infection and Metabolism. The Effect of the Removal of Tonsils and Adenoids on the Nitrogen Balance and Basal Metabolism. J. Pediat., *12*:563, 1937.
2. Johnston, J. A.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth. II. Effect of Thyroid on Calcium Retention. Am. J. Dis. Child., *58*: 1186, 1939.
3. Johnston, J. A.: Nutritional Studies in Adolescent Girls. Springfield, Ill., Charles C Thomas, 1953.
4. Johnston, J. A., and Howard, P. J.: The Celiac Syndrome. J. Pediat., 35:1, 1949.
5. Krogman, W. M.: A Handbook of the Measurement and Interpretation of Height and Weight in the Growing Child. Monographs, Society for Research in Child Development, XIII, No. 3, 1948.
6. McCune, D. J.: Dwarfism. Clinics, *2*:380, 1943.

Henry Ford Hospital
Detroit 2, Michigan

ENLARGEMENT OF BREASTS DURING CHILDHOOD

MATTHEW M. STEINER, M.D.

Enlargement of the breasts during childhood may be the result of any of a number of etiologic factors. These factors are outlined in Table 21.

TABLE 21. *Classification of Etiologic Causes of Enlargement of Breasts during Childhood*

I. PHYSIOLOGIC ENLARGEMENT
A. Newborn
B. Adolescent
II. ENLARGEMENT ASSOCIATED WITH ENDOCRINE CHANGES RESULTING IN:
A. True precocious puberty
1. Hypothalamic lesions—tumors, cysts, postencephalitis and postmeningitis
2. "Idiopathic"
a. Constitutional precocity
b. Polyostotic fibrous dysplasia (Albright's syndrome)
B. Pseudoprecocious puberty
1. Ovarian—granulosa cell tumor, follicle cysts, miscellaneous tumors
2. Adrenal cortical tumors
3. End organ sensitivity—mammaplasia, virginal hypertrophy, puberty, hypertrophy, mastitis gargantuan, macromastia
4. Medicational
III. GYNECOMASTIA IN THE MALE
A. Newborn
B. Adolescent
C. Testicular tumors
D. Klinefelter syndrome
E. Feminizing adrenal cortical tumor
F. Cirrhosis of liver
G. Thyroid disease
IV. MISCELLANEOUS
A. Tumors
B. Pseudohypertrophy

From the Department of Endocrinology, Children's Memorial Hospital, Chicago.

PHYSIOLOGIC ENLARGEMENT

Newborn. Both male and female infants undergo temporary enlargement of the breasts soon after birth (Fig. 28).[22] This so-called pseudoprecocity of the newborn may be associated with the secretion of a small amount of fluid from the breasts, called "witches' milk."[12] Chemical analysis has shown that the neonatal mammary secretion is much like that of ordinary colostrum.[8] In microscopic sections of the newborn hypertrophied breast[15] the major changes are hypertrophy and secretory

Fig. 28. "Pseudoprecocity of the newborn" infant, age 5 days, with symmetrical diffuse enlargement of breasts from which a small amount of secretion ("witches' milk") exuded.

activity of the duct system and active vascular stroma (Fig. 29). The postnatal activity is followed by involutional changes (more marked in the male than in the female) which consist of shrinkage of the duct epithelium with desquamation of the lining cells, narrowing or collapse of the lumens of the ducts and hyalinization or collagenous change in the periductal connective tissue (Fig. 30).

Neonatal breast enlargement is associated with other manifestations of target organ sensitivity. Hence, in the female, there occurs prominence of the labia, clitoris and glans clitoritidis. Local alterations are also evident in the external and internal genitalia. Multilayered hypertrophy of the vaginal epithelium, whose cells contain a considerable amount of glycogen,[9, 13] is accompanied by an initial, thin, glairy vaginal

discharge which later becomes thicker and whitish-yellow; changes in bacterial flora and *p*H are also characteristic of these changes. Uterine enlargement and congestion may be sufficient to produce visible bloody

Fig. 29.

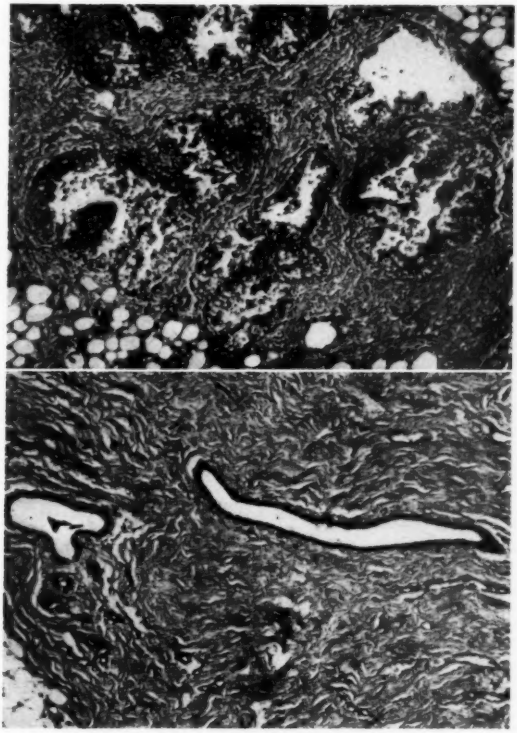


Fig. 30.

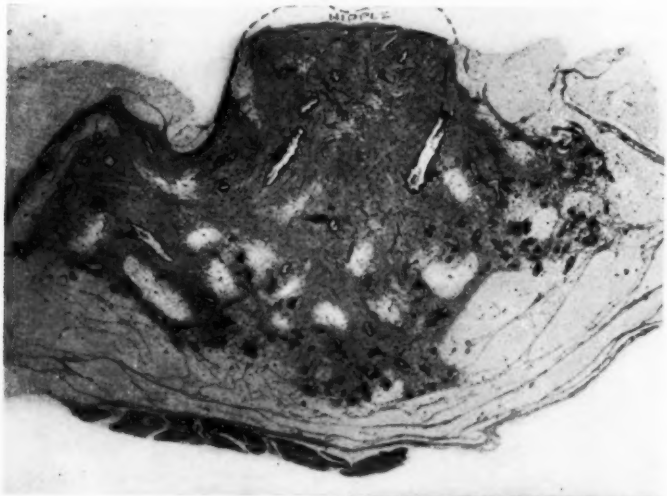
Fig. 29. High power photomicrograph of microscopic section of newborn hypertrophied breast. The mammary tubules are dilated and lined with 2 or more rows of desquamating columnar epithelium. There is round cell infiltration in the vascular stroma. (Charles F. Geshickter: Diseases of Breast. Philadelphia, J. B. Lippincott Company.)

Fig. 30. Photomicrograph of breast of a female infant of 10 months. Quiescent mammary gland during childhood. The mammary tubules are narrow and lined with a single row of flattened epithelium. The surrounding connective tissue is collagenous. (Charles F. Geshickter: Diseases of Breast. Philadelphia, J. B. Lippincott Company.)

discharge in about 10 per cent of newborns. The ovaries may exhibit follicular ripening and luteinization, which are produced in experimental animals as the result of injections of pregnancy urine or anterior pituitary hormone.[33]

The temporary alteration in various target organs, of which the breast is more evident, is attributed largely to stimulation by estrogens of maternal origin. Excess concentration of estrogen in the newborn's blood corresponds closely to that of maternal blood.[34] An excretory tide of estrogens appears in the infant's urine during the first week after

Fig. 31.



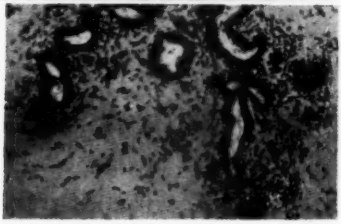


Fig. 32.

Fig. 31. Cross section of female mammary gland of adolescence showing increase in fatty and fibrous stroma and ramification of the mammary tubules. (Charles F. Geshickter: Diseases of Breast. Philadelphia, J. B. Lippincott Company.)

Fig. 32. High power photomicrograph of the section in Figure 31, showing proliferation of basal cells forming lobular buds at the end of the terminal tubules. The periductal connective tissue is increased. (Charles F. Geshickter: Diseases of Breast. Philadelphia, J. B. Lippincott Company.)

birth and diminishes toward the end of this period.[28] Prolactin, which is demonstrable in urine of infants before and during the period of lactation, probably plays a role in the secretion of "milk" by the infant breast. Whether this hormone is fetal or maternal in origin is unknown. It has been suggested that release of prolactin from the infant's pituitary may

be stimulated by the rapid fall in blood estrogen concentration after birth.[14, 25, 32]

In some infants breast enlargement appears excessive—the areas are firm, red and tender. Usually these subside spontaneously and can be protected with sterile gauze or cotton. They are not to be massaged, compressed or anointed. In exceptional cases dilated ducts containing inspissated secretion may become infected ("mastitis neonatorum"), and the management consists of warm compresses, antibiotics and occasionally surgical drainage.

Adolescent. The discussion here will deal with changes in the female. Alterations in the male breast will be dealt with below under Gynecomastia in the Male. The differentiation of the breasts at or prior to adolescence consists in an elaboration of the duct system, an increased deposition of fatty tissue, development of the primary areola and increased growth of the nipple. Macroscopically, adolescent breast enlargement has been divided into three stages: (1) bud stage—elevation of the areola, causing embedding of the papillae in a small conical protuberance on a flat chest; (2) primary breast stage—infiltration of fatty tissue under and surrounding the areola with further elevation and embedding of the nipple; (3) secondary or mature breast stage—more fat in the breasts with elevation of the nipple and development of the ductile system. These changes generally take place between the ages of nine and 13 years, usually before the appearance of pubic hair, and may begin in one or both breasts. At menarche the breast may be at the primary or even third stage of development.

Histologically,[16] the increase in size of the breast is due mainly to increase in fibrous stroma and deposition of fat. There is also elongation, branching and dilatation of the duct tree. The lining cells of the ducts are increased, and knobs of basal cells (lobular buds) appear at the ends (Figs. 31 and 32). The branching and lengthening of the duct tree are accompanied by further dilatation and later by secretion. The lining cells enlarge and stand out individually. The connective tissue undergoes further growth, and adipose tissue accumulates within the stroma. This stage extends up to menstruation and ovulation (Figs. 33 and 34).

It is worth remembering that adolescent breast enlargement may be unilateral at first and may be associated with pain, redness and striae surrounding the nipple. Such patients need reassurance and at times analgesics for relief. There may also occur exaggerated overdevelopment at this time of maturation with marked engorgement and pain (see Mammoplasia). Proper brassiere and analgesics as well as cold compresses can be used. Small discrete lumps in the immature breasts may be palpated; these are usually cystic glandular radicles and are rarely malignant. They should be watched, however.

ENLARGEMENT ASSOCIATED WITH ENDOCRINE CHANGES

True Precocious Puberty

Hypothalamic Lesions. Disturbances in the hypothalamic region may be the result of tumors,[6, 21, 31, 35] cysts, encephalitis[11] and meningitis. Enlargement of breasts occurs as a part of an isosexual precocity in the female and is said to arise from stimulation of gonadotropic ac-

Fig. 33.

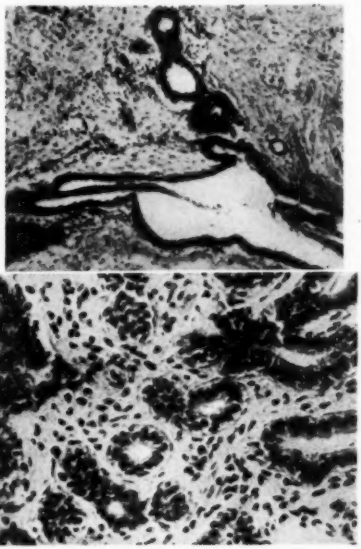


Fig. 34.

Fig. 33. Growth of the mammary tubules at the end of adolescence. Photomicrograph shows continued branching and budding of the terminal tubules. (Charles F. Geshickter: Diseases of Breast. Philadelphia, J. B. Lippincott Company.)

Fig. 34. High power photomicrograph showing the mammary lobules in the premenstruum. The tubules are dilated, contain small amounts of secretion, and are lined by well nourished epithelium. The connective tissue is cellular and contains wandering cells. (Charles F. Geshickter: Diseases of Breast. Philadelphia, J. B. Lippincott Company.)

tivity of the pituitary. Though the exact location of centers in the hypothalamus which give rise to such stimuli is not definitely established, it has been suggested that there are "sex centers" which may be the site of such stimuli.[35] Signs of an intracranial lesion may be present, minimal or absent (Fig. 35).

Idiopathic. Breast enlargement is part of an isosexual precocity due to premature activation of the pituitary of unknown origin. Up to 90

Fig. 35. Two year old girl with hamartoma in hypothalamus and floor of third ventricle, showing enlarged breasts and pigmentation of areolas. (R. E. Gross: Am. J. Dis. Child., Vol. 59.)

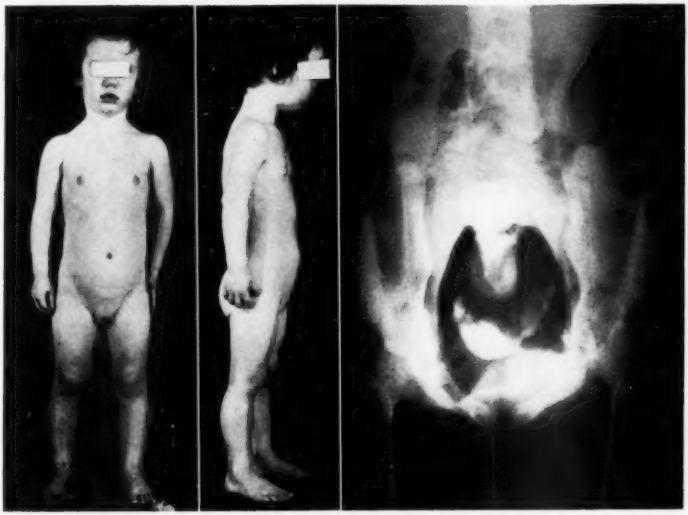


Fig. 36. Idiopathic sexual precocity in a 2 year old girl with enlarged breasts and vaginal bleeding since age 12 months. Bone age normal. Skull negative. No abnormal neurologic findings. 17-Ketosteroid output 0.9 to 1.4 mg. per 24 hours. Moderately cornified vaginal epithelium. Pneumoperitoneum shows normal-appearing internal genitalia with moderately enlarged ovaries.

per cent of cases of isosexual precocity are said to fall into this category.[27] Some cases, few indeed, of isosexual precocity due to hypothalamic tumor may be placed in this group, particularly when signs of expanding intracranial lesion are minimal or absent. Novak[27] refers to this group as "constitutional type of sexual precocity" and suggests that the pituitary activation may depend upon some abnormal genetic factor

Fig. 37. Peruvian child, age 5 years and 6 months, developed sexually and menstruated at 3 years. Menses occurred regularly until onset of pregnancy at 4 years and 10 months. At 5 years and 7 months she was delivered by cesarean section of a boy weighing 6½ pounds. (E. Escomel: La Presse Médicale, Vol. 47.)

(Fig. 36). The famous case often referred to is that reported by Escomel[10] of a Peruvian girl who menstruated at three years, and in 1939, at age five and a half years, gave birth by cesarean section to a 6½-pound boy (Fig. 37).

POLYOSTOTIC FIBROUS DYSPLASIA. McCune and Bruch[26] and later Albright[1, 2] and others have described in girls a syndrome in which sexual precocity is associated with areas of increased pigmentation and disseminated areas of osseous rarefaction, termed "polyostotic fibrous dysplasia." The etiology is not definitely established (Fig. 38).

Fig. 38. Polyostotic fibrous dysplasia (Albright's syndrome) in a 2½ year old girl, showing enlarged breasts, skin pigmentation and fibrous dysplasia of skeleton. Vaginal bleeding and pubic hair appeared at 14 months.

Pseudoprecocious Puberty

In contrast to the normal but precocious puberty of intracranial or pituitary origin, these disturbances exhibit no real establishment of gonadotropic activity of the pituitary, and hence the gonads do not show normal maturation or gametogenic function.

Fig. 39. Seven year old girl prior to removal of granulosa cell tumor of the ovary, showing precocious enlargement of breasts and heavy growth of pubic hair. (P. B. Bland and L. Goldstein: Surg., Gynec. & Obst., Vol. 61.)

Ovarian. The secretion of estrogen from granulosa cell tumor, follicle cysts and miscellaneous tumors such as chorioepithelioma and teratoma is responsible for the adolescent development of the breasts, vagina and uterus. In 20 cases of granulosa cell tumor which Geshickter[17] collected the patients' ages ranged from 19 months to 12 years. Mammary hypertrophy was associated with precocious menstruation, increase in stature and growth of external genitalia and sexual hair. In the case of Bland and Goldstein[4] the mammary hypertrophy and menses regressed with removal of a granulosa cell tumor of the ovary, but reappeared with recurrence of the tumor in the second ovary, and again disappeared

with removal of the second ovary. Thus it was demonstrated that the endocrine activity of the tumor was the cause of the sexual precocity.

The enlargement of the breasts in all the collected cases is described as diffuse, symmetrical and rounded and simulating the normal mature breast. Since the enlargement is the result of elaborated estrogen, it is reasonable to conclude that it is identical with that of normal puberty consisting in growth of duct and periductal connective tissue and infiltration of adipose tissue (Fig. 39).

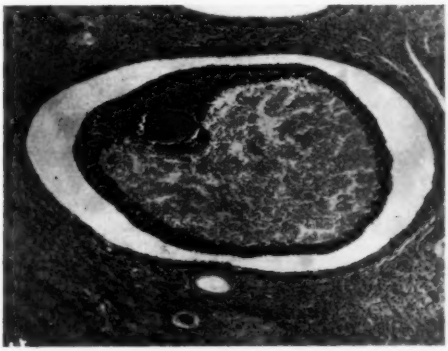


Fig. 40. High power photomicrograph of microscopic section of ovary showing complete follicle with secretory germinal epithelium. Many such follicles were noted to harbor normal-appearing ova. No corpus luteum was seen.

Case History. The endocrine manifestations of follicle cysts is illustrated by the history of an infant who had vaginal bleeding at the age of 6 weeks and again at 2 months. At 3 months of age symmetrically enlarged breasts, resembling those at puberty, were associated with the appearance of pubic hair. The bone age was normal. The sella turcica was not unusual, and there were no abnormal intracranial findings. The output of 17-ketosteroids was 0.55 mg. in 24 hours. The pregnanediol value was 0.08 mg. in 24 hours, and the vaginal cells were moderately cornified. Large follicle cysts were found in both ovaries (Fig. 40); after their removal the breasts regressed, and there has been no further vaginal bleeding.

Mammary hypertrophy has been described in association with chorioepithelioma and teratoma of the ovary. Such sexual precocity was first described in 1904 by Pick,[29] who, in an autopsy on a nine year old girl with precocious puberty and mammary development, found chorioepithelioma of the ovary.

Adrenal Cortical Tumor. Bulloch and Sequeira[7] in 1905 reported sexual precocity with fully developed breasts in a girl of nine years and nine months. At autopsy there was a tumor of the adrenal cortex with metastases. Young[37] in 1937 reported a four year old girl with enlarged breasts and pseudohermaphrodism resulting from hyperplasia of the adrenal cortex. The estrogen value was markedly increased and fell to low levels

after operation. At present it is fairly well established that the adrenal cortex, in addition to elaborating androgens, can under certain conditions secrete estrogens. The case reported by Wilkins in a male will be discussed under Gynecomastia in the Male.

End Organ Sensitivity. This fairly common type of breast enlargement ("mammoplasia") may occur at any age and is part of an idiopathic type of sexual precocity. This may occur at infancy and may not be associated with precocious menarche or sexual hair. Such changes

Fig. 41. End organ sensitivity in a 2 year old girl with symmetrically enlarged breasts. The breasts resemble those developing during pubescence. There was no associated sexual hair or vaginal bleeding. This child was followed up through puberty and had a normal menarche.

are probably the result of end organ or target organ sensitivity to normal hormonal output from the pituitary. In such children there is usually no intracranial lesion or endocrinopathy. Though some psychologic difficulties may develop because of the enlarged breasts at a very early age, such children have been followed up through adolescence without other stigmata of sexual precocity (Fig. 41).

Occasionally the breasts show most unusual enlargement at puberty. Gillespie and Hurter[19] described such enlargement under "virginal hypertrophy of breasts" in a 12 year old girl, without menarche, whose vaginal smear showed few mature epithelial cells with scant glycogen content. The breast was removed for cosmetic reasons, and on micro-

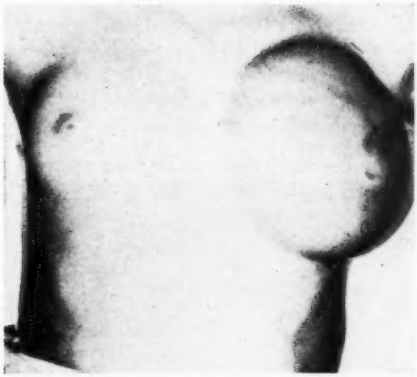


Fig. 42. "Virginal hypertrophy of breast" in a 12 year old girl without menarche. (J. B. Gillespie and A. J. Hurter: J. Pediat., Vol. 35.)

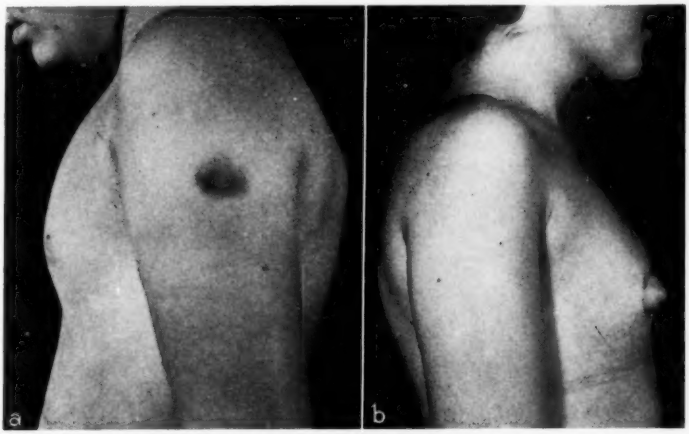


Fig. 43. Ovarian agenesis in a 15 year old girl. Diethylstilbestrol was administered for cosmetic reasons. *a*, Before and, *b*, after medication.

scopic examination the lining ducts were thickened and the interstitial connective tissue was markedly increased (Fig. 42). The etiology of such extreme enlargement, while not definitely established, may also be said to result from "end organ sensitivity." Other names have been given to this condition, e.g., puberty hypertrophy, hypertrophy of adolescence and macromastia.

Medicational. Diethylstilbestrol has been administered to patients with ovarian agenesis to bring about enlargement of the breasts for cos-

metic reasons (Fig. 43). Prouty[30] described a four year old boy who had enlarged breasts from exposure to stilbestrol dust adherent to the clothes of his mother, who worked in a packaging plant (Fig. 44).

GYNECOMASTIA IN THE MALE

Newborn. As in the female infant, analogous changes are seen in target organs of the male infant with enlarged breasts. These consist of squamous metaplasia of the epithelium of the utricle, prostatic urethra and at times with focal hyperplasia of prostatic acini.

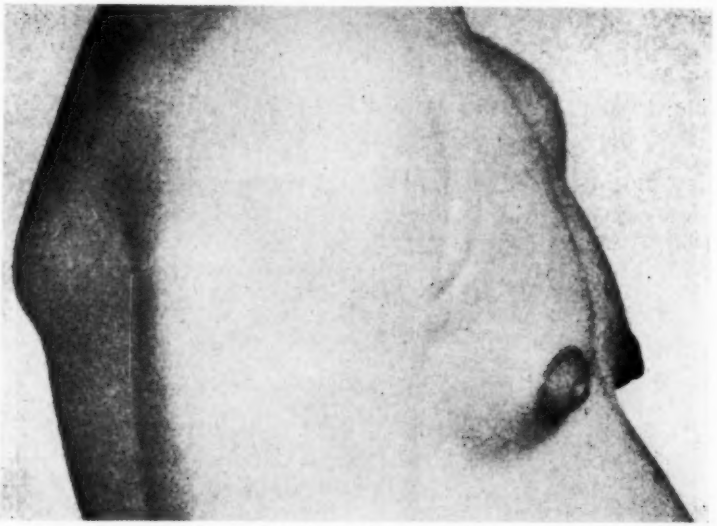


Fig. 44. Four year old boy with enlarged breasts following exposure to stilbestrol. (M. Prouty: Pediatrics, Vol. 9.)

Adolescent. Breast enlargement in the male adolescent may be unilateral or bilateral, generally persists for 18 months, and gradually subsides. One may see a subareolar node as early as six years of age. There may be some pain or sensitivity of the nipple, which in some cases may be severe enough to bring about psychologic disturbances. Histologically, there is little hyperplasia of the ducts, but considerable periductal fibrous stroma. The etiology of this enlargement is not definitely established. It is possible that estrogens are secreted in excess by the adrenals or testes and that there is a temporary disproportion between the testicular androgen and the hypothetical hormone of the seminiferous tubules, "inhibin." Generally, gynecomastia develops in boys who are very muscular and are undergoing rapid virilization at adolescence. No hormonal

therapy is indicated. Surgical removal may be advised in extreme cases for cosmetic and psychologic reasons (Fig. 45).

Jung and Shafton,[23] on the basis of examination of normal boys and men between the ages of nine and 45, found that the presence of a palpable node, the "subareolar node," was an integral part of adolescence. They concluded from their studies that the average subareolar node be-

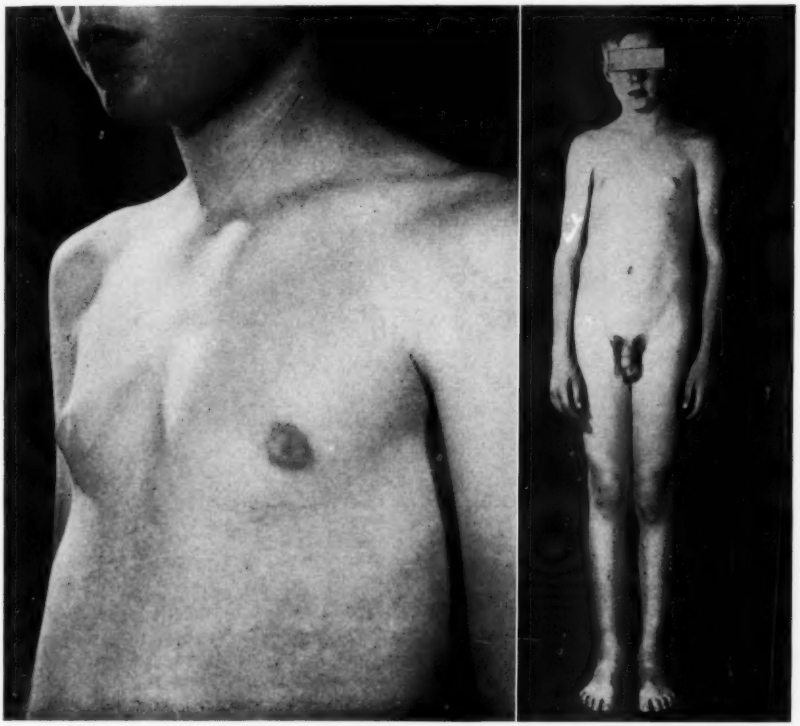


Fig. 45. Adolescent breast enlargement (unilateral) in an adolescent male, with pain and tenderness in the enlarged breast.

gins to grow at about age 13 years, requires 15 months to reach maximum, remains there for 15 months, and slowly declines at age 17 years. Some nodes persist to age 30 years.

Testicular Tumors

There may be hypertrophy of the breasts in patients with tumors of the testes, but these have been encountered only in postadolescent males. Gilbert[18] divided his cases into choriogenic and physiologic types.

In choriogenic gynecomastia the etiology is presumably due to estrogen secreted by the chorioepithelioma. The breasts may secrete, the areolas are enlarged and pigmented, and estrogen and gonadotropin titers are high. The physiologic type of gynecomastia occurs with other tumors such as seminomas, teratomas and interstitial cell tumors. Here the breasts do not secrete, the areolas are not enlarged or pigmented, and the gonadotropin titer in the urine is only moderately elevated. This form is probably secondary to atrophy of the remainder of the testis and frequently occurs after roentgen therapy has been given postoperatively. As such, it is probably related to Klinefelter's syndrome.

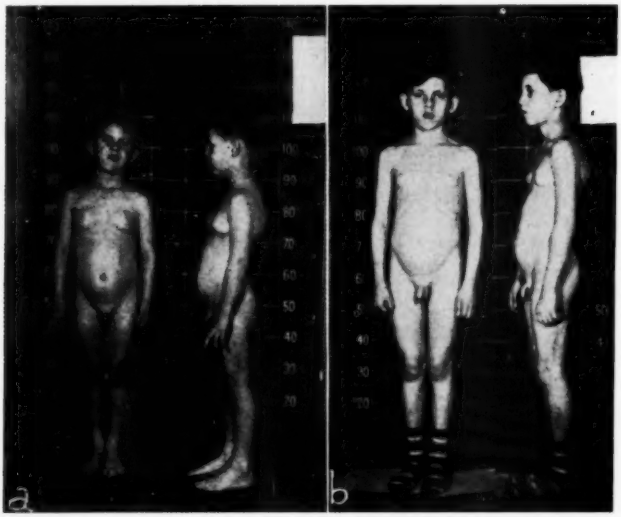


Fig. 46. *a*, Feminizing adrenal tumor in 5 year old boy before operation, showing well developed breasts and normal male genitalia. *b*, At age 8½ years, 3 years after operation, the breasts are much smaller and there are no signs of puberty. (L. Wilkins: J. Clin. Endocrin., Vol. 8.)

Klinefelter's Syndrome

This syndrome was described in the postadolescent by Klinefelter, Reifenstein and Albright[24] and is characterized by gynecomastia, aspermatogenesis without A-Leydigism and increased excretion of FSH. These authors postulate that, normally, FSH of the pituitary stimulates the seminiferous tubules to produce spermatozoa and "X"-hormone ("inhibin"). This "inhibin" is analogous to estrin in that it inhibits FSH and stimulates LH production. LH stimulates Leydig cells to produce androgen, which in turn, like progestin, inhibits LH production. In this syndrome the lack of inhibitory effect of "inhibin" on FSH and

not the lack of androgen is the mechanism leading to overproduction of FSH. However, the cause of gynecomastia in this syndrome is not clearly defined.

Feminizing Adrenal Cortical Tumor

Though enlarged breasts in this condition have usually been described in adults, Wilkins[36] described a five year old boy with probably an estrogen-producing tumor of the adrenal cortex. There was no evidence

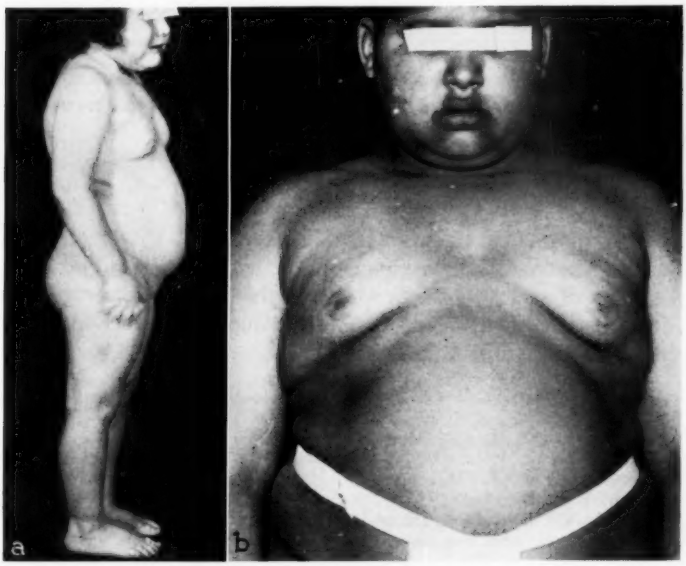


Fig. 47. *a*, Three year old obese girl with adipose tissue infiltration in breasts ("pseudohypertrophy"). *b*, Eight year old boy with adipose tissue infiltration in breasts ("pseudohypertrophy").

of abnormal virilization, and the excretion of 17-ketosteroids was low. The breasts differed from those of the normal female in containing a large amount of connective tissue stroma with little proliferation of the ducts (Fig. 46).

Cirrhosis of Liver

Such cases have been described in the postadolescent. Glass, Edmondson and Soll[20] stressed the development of atrophic testes in their cases and believed that the gynecomastia was secondary to failure of the liver to metabolize estrin.

Thyroid Disease

Several instances of gynecomastia and hyperthyroidism have been described both before and after antithyroid medication by Berson and Schreiber.[3] Bronstein[5] studied a 14 year old boy with bilateral gynecomastia and bilateral aberrant thyroid which contained a papillary adenocarcinoma. The etiology of enlarged breasts in association with thyroid disturbances is not established.

MISCELLANEOUS

Tumors

Though it is possible that enlargement of the preadolescent breast may be the result of benign or malignant tumor, such instances are indeed rare.

Pseudohypertrophy

This apparent enlargement of the breasts may occur symmetrically in either the male or female in association with a generalized obesity, and is the result of adipose tissue deposited in the breasts without glandular or duct changes. The breasts diminish along with reduction in total body weight (Fig. 47).

REFERENCES

1. Albright, F.: Polyostotic Fibrous Dysplasia; A Defense of the Entity. J. Clin. Endocrinol., *7*:307, 1947.
2. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females; Report of 5 Cases. New England J. Med., *216*:727, 1937.
3. Berson, S. A., and Schreiber, S. S.: Gynecomastia and Hyperthyroidism. J. Clin. Endocrinol., *13*:1126, 1953.
4. Bland, P. B., and Goldstein, L.: Granulosa Cell and Brenner Tumors of the Ovary. Surg., Gynec. & Obst., *61*:250, 1935.
5. Bronstein, I. P., and Cassorla, E.: Breast Enlargement in Pediatric Practice. M. Clin. North America, *30*:121, 1946.
6. Bronstein, I. P., Luban, J. A., and Marvelis, N. B.: Sexual Precocity Associated with Hyperplastic Abnormality of Tuber Cinereum. Am. J. Dis. Child., *64*:211, 1942.
7. Bulloch, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs. Tr. Path. Soc. London, *56*:189, 1905.
8. Davies, W. L., and Moncrieff, A.: Composition of Milk from Breasts of Newly-born Infants. Biochem. J., *32*:1238, 1938.
9. Dobszay, L.: Hormonal Reactions of Pregnancy. Am. J. Dis. Child., *56*:1280, 1938.
10. Escomel, E.: La plus jeune mère du monde. Presse méd., *47*:744, 875, 1939.
11. Ford, F. R., and Guild, H.: Precocious Puberty Following Measles Encephalitis and Epidemic Encephalitis, with a Discussion of the Relation of Intracranial Tumors and Inflammatory Processes to the Syndrome of Macrogenitosomia Praecox. Bull. Johns Hopkins Hosp., *60*:192, 1937.

12. Forssell, P.: Klinische und histologische Untersuchungen über die sag. Hexenmilchsekretion mit besonderer Berucksichtigung inhals Verhalten zum Geburtsgewicht des Kindes. Acta paediat., 23 (Supp. 1): 1, 1938.
13. Frankel, L., and Papanicolaou, G. N.: Growth, Desquamation and Involution of Vaginal Epithelium of Fetuses and Children, with Consideration of Related Hormonal Factors. Am. J. Anat., 62:427, 1938.
14. Geist, S. H., and Spielman, F.: Estimation of Anterior Pituitary-Like Hormone in Cord Blood. Proc. Soc. Exper. Biol. & Med., 31:662, 1934.
15. Geshickter, C. F.: Diseases of the Breast. Philadelphia, J. B. Lippincott Company, 1943, p. 17.
16. Geshickter, C. F.: Op. cit., p. 21.
17. Geshickter, C. F.: Op. cit., p. 100.
18. Gilbert, J. B.: Studies in Malignant Testes Tumors. II. Syndrome of Choriogenic Gynecomastia. J. Urology, 44:345, 1940.
19. Gillespie, J. B., and Hurter, A. J.: Virginal Hypertrophy of Breast. J. Pediat., 35: 240, 1949.
20. Glass, S. J., Edmondson, H. A., and Soll, S. N.: Sex Hormone Changes Associated with Liver Disease. Endocrinology, 27:749, 1940.
21. Gross, R. E.: Neoplasms Producing Disturbances in Childhood. Am. J. Dis. Child., 59:579, 1940.
22. Joseph, S.: Zur Biologie der Brustdrüse beim Neugeborenen. Monatschr. f. Geburtsh. u. Gynäk., 83:219, 1929.
23. Jung, F. T., and Shafton, A. L.: Mastitis, Mazoplasia, Mastalgia, and Gynecomastia in Normal Adolescent Males. Illinois M.J., 73:115, 1938.
24. Klinefelter, H. F., Jr., Reifenstein, E. C., Jr., and Albright, F.: Syndrome Characterized by Gynecomastia, Aspermatogenesis, without A-Leydigism and Increased Excretion of Follicle-Stimulating Hormone. J. Clin. Endocrinol., 2:617, 1942.
25. Lyons, W. R.: Hormone Basis for "Witches' Milk." Proc. Soc. Exper. Biol. & Med., 37:207, 1937.
26. McCune, D. J., and Bruch, H.: Osteodystrophia Fibrosa; Report of a Case in Which the Condition Was Combined with Precocious Puberty, Pathologic Pigmentation of the Skin and Hyperthyroidism, with a Review of the Literature. Am. J. Dis. Child., 54:806, 1937.
27. Novak, E.: The Constitutional Type of Precocious Puberty, with a Report of 9 Cases. Am. J. Obst. & Gynec., 47:20, 1944.
28. Philipp, E.: Sexualhormone, Plazenta und Neugeborene. Zentralbl. f. Gynäk., 53:2386, 1929.
29. Pick, L.: Das Epithelioma Chorioektodermale, ein Beitrag zur Lehre von den congenital angelegten Geschwülsten. Berl. klin. Wchnschr., 41:158, 1904.
30. Prouty, M.: Enlarged Breasts from Stilbestrol Exposure. Pediatrics, 9:55, 1952.
31. Seckel, H. P. G.: Precocious Sexual Development in Children. M. Clin. North America, 30:183, 1946.
32. Sklow, J.: Is the Human Placenta Permeable to Gonadotropic and Estrogenic Hormones? Proc. Soc. Exper. Biol. & Med., 49:607, 1942.
33. Smith, C. A.: The Physiology of the Newborn Infant. 2d ed. Springfield, Ill., Charles C Thomas, 1951, p. 297.
34. Soule, S. D.: Presence of Estrogenic Hormones in Maternal and Fetal Circulation. Am. J. Obst. & Gynec., 35:309, 1938.
35. Weinberger, L. M., and Grant, F. C.: Precocious Puberty and Tumors of the Hypothalamus; Report of a Case and Review of the Literature, with a Pathophysiologic Explanation of the Precocious Syndrome. Arch. Int. Med., 67:762, 1941.
36. Wilkins, L.: Feminizing Adrenal Tumor in Male. J. Clin. Endocrinol., 8:112, 1948.
37. Young, H. H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases. Baltimore, Williams & Wilkins Company, 1937.

6354 North Broadway
Chicago 40, Illinois

HEADACHE, IRRITABILITY AND FATIGUE

HADDOW M. KEITH, M.D.

Headache in children is an accompaniment of many intracranial and generalized disorders, but it is a symptom only and does not indicate a diagnosis. It frequently occurs in febrile disturbances due to extracranial infection and in inflammatory or neoplastic processes in the brain or meninges. It may be a sign of unnecessary fatigue, or a reaction to family or school difficulties, or to worries or fears of whatever nature. When a child complains of recurring headache and is not acutely ill, most parents and physicians suspect that there is an abnormality in the eyes, infection in the nose or throat, or that the child may have an intracranial neoplasm.

When headaches are present with acute or severe chronic illness, the accompanying symptoms and signs usually far outweigh the headaches in significance, at least from the diagnostic viewpoint. This is true in meningitis due to any acute infection, in encephalitis of epidemic or sporadic type or that following contagious disease, in the encephalopathies such as lead poisoning, in acute nephritis, in hepatic cirrhosis and in many cases of brain tumor. However, children are frequently brought to their physician because of recurring headache which is practically their only symptom. Parents often add that the child is easily upset, irritable and tires more quickly than his playmates. In such cases it is usually difficult to find the cause or causes and to eliminate them.

ETIOLOGY

Headache mechanisms have been studied by many workers, and certain factors are now well recognized. Wolff[7] has made extensive obser-

From the Section of Pediatrics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Mayo Foundation in Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

vations and has stated that headaches have their origin as a result of (*a*) stimulation of intracranial structures or (*b*) stimulation of tissues on the outside of and adjacent to the skull. He stated that headaches may be produced by (1) traction on veins and displacement of venous sinuses, (2) traction on or distention of the middle meningeal artery and the larger arteries at the base of the brain, (3) inflammation in or about any of the pain-sensitive structures of the head, or (4) direct pressure by tumors on those nerves containing pain-afferent fibers from the head.

His experiments have shown that headache of extracranial origin may be due to various causes. Examples are as follows: (1) Migraine can be due to distention of the external carotid arteries. (2) Inflammation and engorgement of turbinates, ostia, nasofrontal ducts and nasal spaces are responsible for much of the pain of so-called sinus headache. (3) Diseased teeth and prolonged toothache can cause pain and headache through the fifth cranial nerve connection and by producing sustained contraction of the muscles of the head and neck. (4) Sustained contraction of both intraocular and extraocular muscles associated with excessive effort to accommodate and to produce a clear retinal image may cause discomfort, heaviness or headache. These latter mechanisms, with the exception of migraine, can be referred to as "mechanisms of referred pain," and this type of pain is undoubtedly the chief factor in a considerable number of headaches in children.

If none of these factors can be implicated, it is postulated that headache may be associated with personality and behavior disturbances and can be called "psychogenic headache."

To determine the problems of headache encountered in a large clinic, the records of 100 consecutive children having headache as their main presenting symptom have been studied. This does not include those having major illness such as meningitis, brain tumor, encephalitis, and so forth, since in such cases the headache is a lesser symptom of a well recognized disease and is not indexed as part of the diagnosis.

INCIDENCE

The youngest child said to have headache was two years of age, and the oldest 15 years, the latter because no persons over 15 years of age are examined in the pediatric clinic. There were 61 boys and 39 girls. The predominance of boys over girls has been noted by other authors, but not by all. The number of cases at each year of age is given in Table 22.

It is apparent that relatively few children below nine years of age suffer from recognizable headache. This can be readily understood in view of the fact that the majority of the headaches are due to extra-

cranial causes, such as infections, errors of refraction, migraine, or tensions within the family or school circles.

DIAGNOSIS

The diagnoses are given in Table 23. The majority of the patients were examined in detail by pediatricians and neurologists, and in some cases electroencephalograms were made.

Headaches are frequently described as "frontal," either right or left

TABLE 22. *Age Distribution of Children Having Headaches*

AGE, YEARS	PATIENTS
2	1
3	1
4	4
5	5
6	6
7	4
8	2
9	11
10	13
11	14
12	13
13	10
14	14
15	2
Total	100

TABLE 23. *Diagnosis of Headaches in Children*

DIAGNOSIS	PATIENTS
Infection with fever; probable infection	10
Migraine; probable migraine	43
Etiology unknown	30
Associated with ocular abnormalities	3
Due to fatigue	3
Due to emotion and tensions	5
Associated with behavior problems	1
Associated with allergic disturbance	3
Post-traumatic	1
Associated with persistent sinusitis	1
Total	100

side or both, or as "generalized" without any one area being involved. They do occur in definite locations, however, as noted in Table 24.

Electroencephalograms were recorded in 34 of the 100 cases, and disturbances were found as noted in Table 25.

The cases with diagnoses noted in Table 23 may be considered in separate groups.

Fever and Infection

The cases in which headache is due to fever and infection are readily recognized, may be mild or severe, and disappear within, at most, a few days, coincidentally with the disappearance of the infection. Treatment is directed mainly toward the infection, with symptomatic treatment of the headache.

TABLE 24. *Location of Headache in 100 Cases*

LOCATION	CASES
Frontal (unilateral, bilateral)	54
Frontotemporal	2
Generalized	13
Occipital	4
Unilateral	4
Vertex	3
Bitemporal	3
Temporoparietal	1
Unilateral or bilateral	1
Parietal and occipital	1
Location not noted	14
Total	100

TABLE 25. *Type of Electroencephalogram*

TYPE	CASES
Dysrhythmia, grade 1*	7
Dysrhythmia, grade 2*	11
Dysrhythmia, grade 3*	2
Delta waves, grade 1†	5
Dysrhythmia, generalized	6
Normal tracing	3
Total	34

* Waves that are usually rhythmic, repetitive, and tend to be inhibited by eye opening and accentuated by hyperventilation. Specific wave forms.

Grade 1—minimal; continuous or paroxysmal; amplitude up to 30 microvolts.

Grade 2—moderate; continuous or paroxysmal; amplitude up to 60 microvolts.

Grade 3—specific wave forms, spikes, sharp waves, spike-waves and so forth, diffuse or focal.

† Random slow (0.5 to 4 per second) waves, arrhythmic and nonrepetitive. Amplitude up to 50 microvolts.

Migraine

Forty-three of the 100 children had migraine or migraine-like headaches, and this was the largest group with a stated cause for headache. In many of the cases, however, other diagnoses were associated with migraine, such as hay fever, "psychogenic," obesity, tensions, behavior disturbance, convulsive disorder, vasomotor rhinitis, motion sickness,

fatigue, and so forth. It is possible that some of those children said to have headaches of undetermined origin could also have early migraine. Migraine, of course, is not an easy diagnosis and may be open to question. Nevertheless, most of the patients studied had undergone careful detailed examinations, including neurologic examination, and the diagnosis was the result of well considered, experienced opinion, keeping in mind the diagnostic criteria of periodic headache, usually associated with visual disturbances accompanied by nausea and vomiting and an increased family incidence.

It is of interest that Krupp and Friedman[2, 3] in a similar study found that 75 per cent of their patients had migraine and 17 per cent had tension headache. In the present author's group 43 per cent were diagnosed as having migraine, but in 30 per cent the cause was indeterminate, some of these patients possibly having migraine.

Ocular Abnormalities

The author found only three cases in the 100 studied in which the eyes may possibly have been the cause of headaches. In one case a detached retina was noted as well as a minor refractive error. In another case, in which convulsive disorder was suspected, the refractive error was considered enough to warrant correction. In the third case a compound myopic astigmatism was noted and correction was prescribed, although it was questionable whether headaches were related to refractive error.

In a review of 100 patients examined to determine a need for lenses, Walsh and Harris[6] reported that 50 per cent of child patients were brought for examination because of unrecognized emotional problems. Only one of 46 patients with myopia or mixed astigmatism and hyperopia had headache as a complaint. Of the 54 children with normal vision who had various presenting complaints, 14 had headache as their main difficulty, and these were shown to have emotional problems. The wearing of spectacles did not improve the symptom complex in those children having normal visual acuity, and those children with refractive errors sufficient to depress their visual acuity had few symptoms. On the other hand, Glaser[1] stated that in his experience one of the commonest causes of recurrent headaches in children has been errors of refraction and that such errors can cause migraine. No figures are given.

Fatigue, Tension and Behavior Problems

In the present series there were three cases in which fatigue seemed to be the main factor causing the headaches, five in which emotional disturbances and tensions were pronounced, but only one in which a definite behavior problem occurred. These cases have been grouped

together, since there was, in nearly every case, some doubt in the examiner's mind as to the etiology, as indicated by two or three diagnoses being suggested. Doubt, of course, was also present in some cases in other groups, but among the latter the diagnoses, after detailed examination, were considered to be more definite.

Allergic Disturbances

Three children in the series had headaches associated with allergic disturbances. One had hay fever and headaches, and two had vasomotor rhinitis and headaches. Whether allergic factors were causative in these children could not be determined with certainty, but clinically they were associated, and no other factors were found to account for the symptoms. Glaser[1] called attention to the fact that some cases of migraine in childhood are due to food allergy. He stated that when a history of allergy can be obtained, either personal or familial, it is suggestive but not conclusive in the diagnosis of the etiology of migraine headaches and that offending foods can be found most commonly by means of elimination diets.

Post-traumatic

One child in the present series had post-traumatic headaches. These were described as severe generalized headaches following a fairly severe head injury with concussion, but without fracture of the skull. This child's I.Q. was 78 (borderline), and a pneumoencephalogram showed no recognizable lesion.

Sinusitis

The last child in the series had headaches associated with persistent sinusitis. He also had had a mild head injury (no concussion), but after observation and treatment it was concluded that his headaches were related to exacerbations of sinusitis.

COMMENT AND TREATMENT

Many children with recurring headaches are irritable and may fatigue easily. This is readily understandable as a secondary phenomenon, as will be recognized by those adults who have experienced the same annoying symptom. In cases of behavior disturbance, difficult family situations and psychiatric problems the headaches may be secondary to the irritability and fatigue brought on by the abnormal situation. It is

probably impossible in many cases to know which is primary and which secondary.

It is still axiomatic to say that, if at all possible, the underlying cause of the symptom of headache must be uncovered in order to outline treatment intelligently. The presence of acute infection, sinusitis, encephalopathy, increased intracranial pressure or disease such as nephritis will indicate what treatment may be necessary and possible, and such treatment will usually relieve the headache. Symptomatic treatment, every four hours or as considered necessary by the physician, with acetylsalicylic acid, 1 grain (0.065 gm.) per year of age up to five years, alone or with codeine, codeine and papaverine, or meperidine hydrochloride, may also be helpful, especially when the more specific treatment requires time to exert its beneficial effect.

Headache with Allergic Disturbance

Symptomatic treatment to alleviate allergic disturbances may assist in eliminating the symptom of headache. Glaser[1] suggested that elimination diets are of value in this regard, and Unger and Unger[5] have indicated that chocolate, milk, wheat and pork are the most commonly offending foods.

Headache with Ophthalmologic Abnormalities

Some children can undoubtedly be relieved of recurring headache by correction of refractive errors, although from the work of Walsh and Harris,[6] and in the present author's series, this factor was not found to be of such frequent occurrence as is commonly believed. Nevertheless, a careful examination for refractive errors and strabismus should be done by an ophthalmologist to make certain that these factors are not present or, if present, have been properly treated.

Migraine

Migraine is undoubtedly one of the common causes of recurring headache in children. In a study of 516 allergic children MacKinney and Glaser[4] noted that 1.16 per cent had migraine, and Glaser[1] stated that the incidence of migraine in the pediatric population of this country is probably close to 1 per cent. Friedman and his co-workers have made several studies of headache in children, and each study emphasizes the prevalence of migraine. It has already been noted that Krupp and Friedman[2] found 75 per cent of 100 children with headache to have migraine. These authors have found migraine and tension headaches to be so

much in the majority that they limit their discussion of treatment to these cases only.

Migraine may be treated by acetylsalicylic acid in the dosage stated previously. This treatment has been found effective in about one quarter of the cases. For most cases, however, the combination of 1 mg. of ergotamine with 100 mg. of caffeine (Cafergot) is more effective than acetylsalicylic acid. If the symptoms are not relieved in one-half to one hour, the dose is repeated three or four times at the same interval. After a few trials the effective amount may be determined and may be given at one time. In occasional cases the ergotamine and caffeine may be given in suppositories. Side effects of nausea and dizziness may occur if the amount is large. *Either form of treatment must be given early in the attack—the earlier the better.* Glaser[1] stated that he has found that phenobarbital, ephedrine, the antihistaminics and diphenylhydantoin are of little help in true migraine.

In some cases migraine is apparently related to emotional upsets. These are so varied and depend on so many different factors that each case must be considered on its own merits. The frequent occurrence of migraine in certain families may depend to a considerable extent on the emotional factors within the family situation as well as on hereditary factors. If the migraine is severe and neurotic symptoms or family and behavior disturbances are outstanding, psychiatric treatment will be necessary as a prophylactic measure.

Fatigue, Tensions, Emotional and Behavioral Difficulties

It is perhaps doubtful that fatigue alone accounts for many cases of headache. Three cases were noted on the present series, but while fatigue seemed to be the most definite cause, emotional factors and tensions were also present in some degree. In such a situation, treatment which includes discussion with the parents and a suitable program of activities with extra rest during the day, or longer hours of sleep at night, may suffice.

In the cases in which emotional disturbances and tensions are most outstanding and in those with definite behavior problems, a study of psychologic factors may do much to alter the frequency and severity of headaches. Parental attitudes of rejection combined with strictness and rigidity in training may need explanation to, and understanding by, the parents and subsequent modification. The child's need for affection, and his assertiveness and aggression, in conflict with parental rigidity, may result in hostility, feelings of inadequacy and guilt. If these are combined with fatigue due to too many social and athletic or scholarly activities and anxieties, recurring or persistent headaches may occur.

A thorough examination with elimination of the possibility of recognizable disease, such as infections, brain tumor, ophthalmologic abnormalities or systemic disease, will do much to reassure parents whose children have repeated headaches. A discussion of psychologic factors, with readjustment on the part of parents and perhaps changes in the child's environment, can both reassure parents and improve the patient's symptoms. Such effects cannot usually be achieved at one visit, but the amount of time necessary may not be excessive, and the results may be gratifying. If the psychologic factors and abnormalities of behavior are considerable, and no progress is made in a reasonable period of time, psychiatric consultation and more extensive psychotherapy will be necessary. This should be undertaken by one who is trained in the fundamentals and techniques of child psychiatry.

REFERENCES

1. Glaser, J.: Migraine in Pediatric Practice: Observations with Special Reference to Migraine of Allergic Origin. Am. J. Dis. Child., 88:92, 1954.
2. Krupp, G. R., and Friedman, A. P.: Recurrent Headache in Children: A Study of 100 Clinic Cases. New York State J. Med., 53:43, 1953.
3. Krupp, G. R., and Friedman, A. P.: Migraine in Children: A Report of Fifty Children. Am. J. Dis. Child., 85:146, 1953.
4. MacKinney, L. G., and Glaser, J.: Incidence and Progression of Allergic Syndromes in Children. Unpublished data.
5. Unger, A. H., and Unger, L.: Migraine Is an Allergic Disease. J. Allergy, 23:429, 1952.
6. Walsh, F. M., and Harris, L. D.: Ophthalmic Headache: Headache among Children. Journal-Lancet, 71:530, 1951.
7. Wolff, H. G.: Headache and Other Head Pain. New York, Oxford University Press, 1948, pp. 584–585.

Mayo Clinic
Rochester, Minnesota

THE FAINTING CHILD

M. G. PETERMAN, M.D.

The term "fainting child" is admittedly ambiguous, but Dr. John Bigler, who suggested the title, had in mind an all-inclusive term which would cover all cases of syncope, loss of consciousness or control, and minor convulsions. The family physician who sees most of these problems first must get a complete description of the incident and then consider the possibilities in order. The first factor that must be considered is the patient's age; the second, the circumstances or stimuli coincident with, or preceding, the "fainting spell." It is then important for the physician to obtain as much information as possible concerning the family history.

FAINTING SPELLS

The true faint is usually due to a sudden shock or emotional disturbance or accident or the sight of blood or to sudden pain. The child becomes pale or gray, complains of nausea or dizziness, and collapses, usually without injury or pain. The pulse is rapid and weak, the blood pressure low. Recovery is usually prompt when cold water is applied to the face and the patient placed in the reclining position with the head low. The condition is due to defective vascular reflex regulation. True fainting spells, or syncope, occur most commonly in the young teen age girls who usually give a family history of fainting spells.

CASE I. This may be considered a typical case in point. A 12 year old girl was referred to me because of "fainting spells." Her mother was a well trained, stable nurse. The child had had nausea every morning from 3 to 8 years of age. Shortly after, her fainting spells began, usually preceded by "butterflies in the stomach." She would faint whenever strangers appeared in her home or when she was taken to the doctor for an examination. There was nothing unusual in her past history. Her menstruation had begun 5 weeks before she was brought to me. Physical examination was essentially normal except that the child had a fatigue posture and fainted twice on the examining table while I was taking her blood pressure. When she recovered, her blood pressure was 100/70. The urine in the afternoon showed a 2 + albumin with no formed elements. The morning specimen on arising was normal. The blood cell count was normal. Sedimentation rate was normal. Blood Wassermann was negative. An electroencephalo-

gram was done and a satisfactory tracing obtained. This showed no abnormality. Instructions were given for the correction of the fatigue posture, and a shoulder brace was prescribed. There were no further attacks.

Fainting spells may occur in younger children, as, for instance, in Case II.

CASE II. A 2½ year old girl was referred to me by her family physician because she had had fainting spells for 4 months on the average of one a month. She complained first of a stomach ache, then had cold sweats, which lasted for 10 or 15 minutes. These attacks always occurred in the morning on arising. She was not unconscious at any time and never lost sphincter control. In one attack the eyes rolled. On physical examination nothing abnormal could be found. The urine was negative or normal. The blood cell count was normal. Sedimentation rate was normal. Roentgenograms of the wrists showed a normal bone age and maturation. The blood pressure was 90/60. Two electrograms at one week intervals were both normal. The blood sugar was 106 mg. Within one month the fainting attacks ceased and never recurred.

CASE III. Another girl was referred to me by her family physician. She was 4 years and 8 months of age. The mother stated that the child was hard to manage and had frequent temper tantrums. She had fainted 4 times, always after she had been reprimanded or punished. Examination revealed no abnormality. The blood cell count was normal. Urine was negative or normal. Roentgenograms of the wrists were normal. The electroencephalogram revealed no abnormalities. The mother was advised not to punish the child and to tolerate her behavior disorders. The fainting attacks ceased.

Occasionally boys are affected.

CASE IV. A boy 10 years and 10 months of age was referred by his family physician because of 5 fainting spells which had had their onset at 6 years of age. Two of the spells had occurred in the preceding week. The boy would become limp, lose consciousness for 5 or 10 minutes, and then recover with extreme fatigue. There was no loss of sphincter control. The seizures might occur any time of the day. Examination was essentially normal. Urine was negative or normal. Blood cell count was normal. Sedimentation rate was normal. Roentgenograms of the wrists were normal. Blood sugar was 103 mg. Two electroencephalograms at one month intervals showed no abnormality. The fainting spells disappeared within 6 months and have never recurred.

In the next boy, however, the story was more enlightening and suggestive.

CASE V. An 11 year old boy was referred to me by his family physician because of the following story. Three weeks previously he had fallen from his bicycle on the way to Sunday School. He did not remember falling or any part of the accident. He did not recall why he had gone to Sunday School on a different route than he usually took. He had no bruises, and his clothes were not soiled. The street, however, was icy. After he had recovered consciousness he slept the rest of the day. Physical examination revealed no abnormality. The blood pressure was 110/70. The urine was negative. The blood cell count was normal. Sedimentation rate was normal. Roentgenograms of the wrists were normal. The electroencephalogram revealed spike and wave activity in the right frontal area and 14- and 6-per-second positive spikes in the right temporal area (Fig. 48). These findings usually indicate a focus of epilepsy. The boy was placed on a hydantoin preparation and has had no recurrences.

Temper Tantrums

Children with temper spasms or breath-holding attacks are sometimes able to faint or "pass out" when they are punished or reprimanded or

refused certain requests. This is well illustrated in Case III. Unless the temper tantrums last too long or the child becomes too destructive, it is best to ignore the affairs entirely. The same treatment applies to breath-holding attacks. The infant or child who finds that his misbehavior causes him only to be ignored and neglected soon corrects his behavior. In some cases, however, if the child becomes violent and destructive in his actions and if his attacks recur with some regularity, it is advisable to obtain an electroencephalogram to look for a psychomotor pattern of epilepsy. Many periodically recurring attacks of behavior disturbances

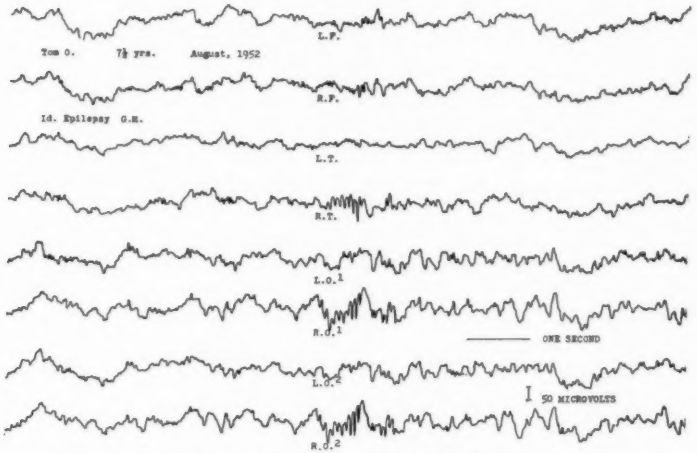


Fig. 48. 14-per-second waves in right temporal lobe. Temporal lobe epilepsy.

in the child are due to psychomotor or thalamic syndrome epilepsy (Fig. 49). They require intensive treatment. The most effective drugs are Phenurone, Mysoline, Benzedrine, Nuvarone and Gemonil.

Phenurone or Phenacemide, which is phenylacetylurea, is a toxic drug which must be used with caution. Infants may be given ¼ tablet every 12 hours, young children ½ tablet every 12 or eight hours, and older children one tablet every 12 or eight hours. The blood cell count must be checked in two weeks and then monthly. The urine must be checked monthly, and any sign of jaundice will require a study of the liver function. In the young adolescent Phenurone may cause a behavior change similar to a psychosis. However, prompt discontinuance of the drug will remove the danger of further toxicity.

Mysoline may be given to infants in ¼ tablet every 12 or eight hours, young children ½ tablet every 12 or eight hours, and older children one

tablet every eight or, if necessary, six hours. There is no toxicity, but occasionally the drug caused disequilibrium or behavior disturbances.

Benzedrine can be given to infants in the powder form, 1 mg. every eight or 12 hours, added to syrup, honey or jelly. In the young child 2 mg. of the powder may be given every eight or six hours as necessary, in the same preparation. For the older child 5-mg. tablets may be given every eight hours after meals to avoid a depression of the appetite. In older children it may be necessary to increase the dose to 10 mg. or to give a 15-mg. long or delayed action capsule in the morning before breakfast.

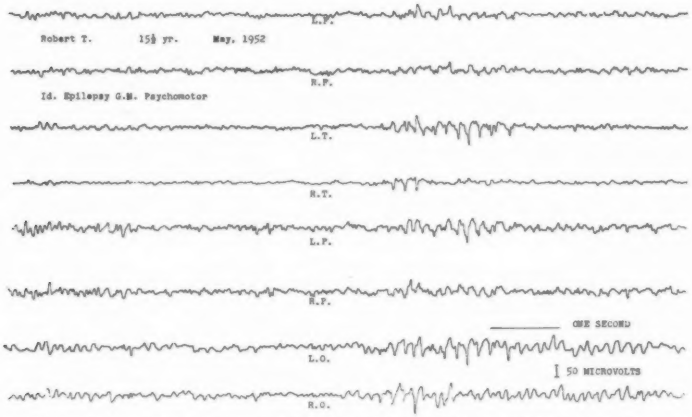


Fig. 49. Positive spikes in temporal lobes. Left temporal and right temporal psychomotor epilepsy.

Nuvarone may be given to infants in a dosage of ¼ tablet, or 0.125 mg. every 12 or eight hours. The young child may be given ¼ to ½ tablet every 12 or eight hours, the older child one tablet every 12, eight or six hours as necessary.

Gemonil is a harmless barbiturate which may be effective. It may be given in doses of 0.016 gm. every 12 or eight hours to infants, 0.032 gm. every 12 or eight hours to young children, and 0.065 gm. every 12 or eight hours to older children.

CAROTID SINUS SYNCOPE

There are rare cases of carotid sinus hyperirritability. In such children a tight collar or compression over either carotid sinus in playing or wrestling may provoke an attack of syncope. The history in such cases is usually typical and self-explanatory.

CARDIAC DISEASE

Children with advanced cardiac disease and low cardiac reserve may faint easily on exertion or unusual excitement. The rare case of Stokes-Adams syndrome will be recognized by an irregularity in attacks and an extremely slow pulse.

CONVULSIONS

Fainting should be distinguished from "blackouts" or sudden collapse. If the older child has an aura, or warning, or a sudden cry or a sudden terror before his collapse, he will probably have a major or a minor con-

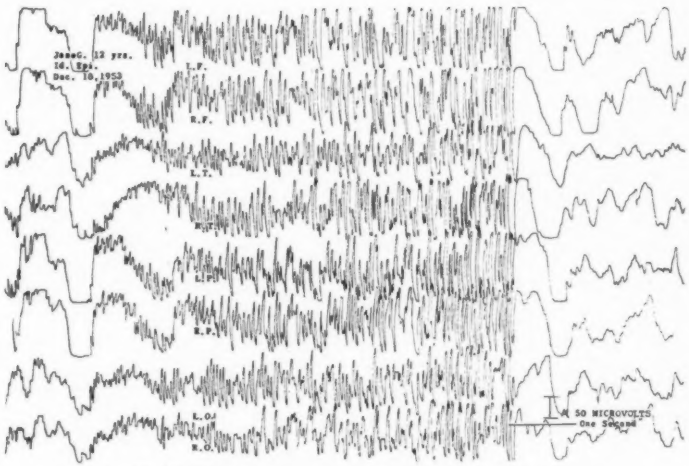


Fig. 50. Grand mal or major epilepsy, subclinical seizure.

vulsion of epilepsy. This is the most important point in the differential diagnosis. The child with petit mal usually has no aura or warning. It is only after months or years of seizures that he recognizes the preliminary feelings or warnings. If he has a true petit mal, the attack is of short duration and he is aware that he has had a seizure. He recovers promptly and continues with his activity. If he has had a grand mal or major attack, the seizure is of longer duration. It is followed by confusion and disorientation, then usually a stupor, deep sleep or drowsiness. The patient with fainting spells or syncope must have a thorough cardiac check-up and testing of the blood pressure in various positions, sitting, standing and lying. A patient with "blackouts" or "passing out," or dizzy spells, should have a careful neurologic examination and then an electroencephalogram.

The infant who suddenly goes limp, becomes quite flaccid and then

has twitchings of one or several groups of muscles and goes into tonic spasms, followed again by drowsiness, stupor or collapse, usually with involuntary loss of sphincter control, has idiopathic epilepsy or a brain injury (Fig. 50). These are extremely serious in that they tend to progress in frequency and severity and do not respond to the usual medications (Fig. 51). The child is not really fainting, but has a rapid loss of consciousness. At times he may throw out his extremities before he falls or drops. He is to be distinguished from the child with myoclonic jerks or myoclonic epilepsy who does not lose consciousness. The electroen-

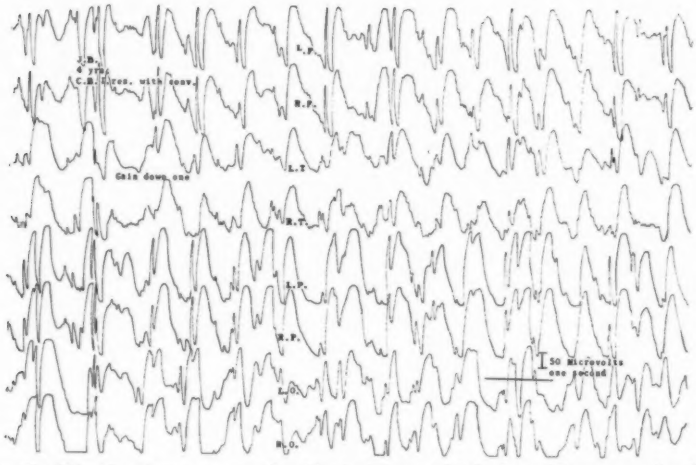


Fig. 51. Akinetic seizures as a result of brain injury at birth. 1- and 2-per-second spike waves.

cephalogram makes a complete distinction possible. The only drugs which have been effective in the treatment of akinetic seizures have been Phenurone and Mysoline. The dosage was mentioned earlier.

The child who suddenly stops his play or other activity and stares off into space, or blinks his eyes or swallows repeatedly, is probably having a petit mal seizure. Though he will seldom injure himself, the petit mal manifestation of epilepsy is most serious because it is most likely to develop into major, or grand mal activity, and it does not respond to the usual drug therapy. The first drugs found to be effective in the treatment of petit mal were Tridione and Paradione. Tridione is available in solution for infants, and the dosage is 0.01 gm. daily divided into three doses, one every eight hours. The older infant may be given 0.02 gm. daily, divided into three doses. For the young child "Dulcets" are available in 0.15-gm. tablets. One tablet may be given every eight hours.

In older children capsules are available in a dosage of 0.3 gm. to be given one every 12 or eight hours as necessary.

Paradione is also available in solution and may be given in the same dosage as Tridione. It is also available in capsules of 0.3 gm. Both these dione drugs are toxic and should be used with caution. Children may complain of visual difficulties which are the result of a "snow blindness." The blood cell count should be checked two weeks after the drug is started and monthly thereafter. The urine should also be checked every month. In case of leukopenia or anemia or other evidence of bone marrow suppression the drugs must be discontinued immediately.

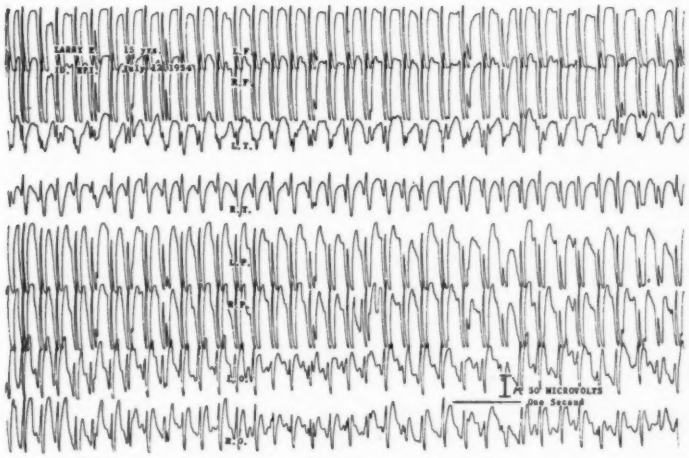


Fig. 52. Typical 3-per-second spike wave of petit mal epilepsy.

It is important to establish the diagnosis of petit mal with the electroencephalogram and particularly to consider the probability that 50 per cent of the children with petit mal also have potential or latent grand mal or major epilepsy (Fig. 52).

HYPOGLYCEMIA

Certain children with low glycogen reserve may have weak spells or go into collapse if they miss several meals or if they vomit. The child who misses his evening meal and then goes to church or school the next morning without food may then faint because his blood sugar has reached a low level. If such a child then has a major convulsion, he is probably an epileptic or has a low convulsion threshold. The hypoglycemia is only the trigger mechanism which sets off the convulsion.

A careful history will provide the indication for a blood sugar determination. Before that, however, a clinical trial with the administration of well sweetened fruit juices or sugar will provide the clue.

CASE VI. An 18 months old boy was referred to me because he had a sudden collapse at 8 A.M. before breakfast and after a light supper the day before. His fasting blood sugar was 69 mg. Sweetened orange juice brought about a prompt recovery. Five months later he had another attack of "fainting" at 6 A.M. the morning after he had missed supper. He was relieved promptly with sweetened orange juice. A blood sugar tolerance curve showed a rather flat curve with prompt utilization of sugar. The mother was advised to give the boy sugar or sweetened fruit juice if he ever missed a meal for any reason. There were no further recurrences. His younger, year old brother had similar attacks and a similar flat sugar curve. He was also promptly relieved with sugar or sweetened orange juice.

HYPOSUPRARENALISM

Mention should be made of Addison's disease, or hyposuprarenalism. The patient with this disease may complain of weakness or fainting spells. He will act similarly to the child with hypoglycemia. The seriousness of his condition will soon be evident, and his prompt response to suprarenal extract by injection or inhalation will indicate the diagnosis.

ELECTROENCEPHALOGRAPHY

The electroencephalograph has been the most useful instrument and laboratory aid ever made available in the study of fainting spells, syncope and attacks of unconsciousness. With this apparatus it has been possible to establish and identify the various types of epilepsy. It is also possible to establish the typical findings in the case of akinetic seizures. Every patient with attacks of syncope or unconsciousness should be submitted to electroencephalography. The patient who faints when the tracing is being obtained may show slow waves in the cortex during the faint. This is probably due to a local vasomotor reaction.

SUMMARY

The patient with true fainting spells or syncope should be treated or kept under observation for at least one year. By that time he usually becomes stabilized and has no recurrences. The patient with hypoglycemia will require carbohydrate or sugar between meals and regular meals for one or more years. A sugar tolerance test at the end of that time will indicate whether he has become stabilized or requires continued treatment. The infant with akinetic seizures will require intensive treatment for at least one year. The patient with petit mal or grand mal epilepsy must be treated with drugs in adequate dosage until he has been free of seizures for at least one year. If his electroencephalogram

is then negative, the dosage may then be reduced by half for the next year. At the end of two years the electroencephalogram should be repeated, if possible, and if entirely negative or normal and if the patient has been known to be absolutely free of seizures, the medication may be tapered off during the third year.

411 East Mason Street
Milwaukee 2, Wisconsin

HEMANGIOMA IN INFANTS

ALFRED B. FALK, M.D.

The hemangioma is a benign tumor consisting of autonomously formed blood vessels. From the standpoint of the clinician the manifestations pertinent to the skin are usually grouped into the following three categories: the nevus flammeus, or the darker "port wine" nevus, primarily a lesion ranging in color from a faint pink to a deep bluish-purple and located at skin level; the nevus vasculosus, commonly called the "strawberry mark," a circumscribed tumor elevated above the surface of the skin and having a reddish-pink to a bright red color with only a moderate degree of extension into the underlying corium; and lastly, the cavernous hemangioma, in which there is a mass present in the subcutaneous tissue, usually circumscribed and frequently elevated and involving the overlying skin. In the last type of lesion the skin may be normal in color or present a bluish cast. On palpation a tumor with some degree of depth, firmness and warmth may be felt. Mixtures of these fundamental types may occur in the same patient or in the same lesion.

DEVELOPMENT

The origin[6] of these tumors has been a matter of study. It has been known for many years that these lesions are autonomous growths consisting of new formations of vessels. The mesenchyma, the source of vascular tissue, through sequestrations gives rise to nests of angioblastic cells separated from the rest of the vascular tree. These are the anlagen which proceed to form the various-sized cords which in turn canalize to form the vessels of the hemangioma. The nests become stunted masses of vessels which intercommunicate and in turn connect to the general circulation. In the discrete, circumscribed, vascular tumor the attempt is made to retain a semblance of a circulation with an afferent and an efferent vessel. A deviation from the foregoing is found in those vascular

growths associated with tremendous enlargement of a limb. In this type of lesion there is an intermingling with other mesodermal derivatives such as muscle, fat and fascia, so that one has difficulty in determining where one factor ceases and another begins.

An attempt to explain the location of the hemangioma on the infant by correlation with the position of the fetus inside the uterus has its supporters. The contention here is that intrauterine pressures are pushing the developing organism against various bony prominences of the maternal pelvis, resulting in trauma to the fetus and eventuating in a hemangioma at the irritated site. Too, many hemangiomas occur in areas developing about fetal clefts, so that some contend that the presence of the clefts influences the appearance of the hemangioma. In passing, it is difficult to omit mention of "old wives' tales," steeped in fancy, attributing the marking of the child to some incident occurring during pregnancy. At best these make intriguing stories.

PATHOLOGY

When examples of these three clinical types of hemangiomas are removed and scrutinized under the microscope, one realizes that there are two basic types. The first is the so-called capillary hemangioma, which fits the nevus flammeus and nevus vasculosus categories, consisting in a marked increase of capillaries in the corium along with dilatation of the vessels. In the second, the cavernous type, there are large irregular spaces filled with blood. These spaces have only a thin lining of endothelium. Newly formed vessels with thick walls containing adventitial cells are prominent. Since endothelial cell proliferation is present in the nevus vasculosus and absent in the nevus flammeus variety, these two similar lesions may be differentiated through microscopy.

CYCLE

Many large series of cases show parallel observations as to incidence, onset, location and course of hemangiomas. These tumors are about twice as common in female infants as in male infants. The vast majority are present at birth or shortly thereafter. Lesions may be multiple. Approximately half the cases of this type present growths located about the head.[1] It is a common experience in infancy to have superficial vascular tumors (capillary type) in the area of the glabella, eyelids or nasolabial sites. These disappear spontaneously in a matter of a few weeks to months, leaving a perfectly intact skin, normal in all respects, at the previously involved site. However, lesions located on the nape of the neck, having a similar appearance, usually persist throughout life.

The hemangioma grows at a rate paralleling that of the child's growth

and frequently at a greater rate. Usually this growth ceases spontaneously and involution occurs, the cycle taking up to six years.[4, 7] When it does not occur, which happens frequently, our therapeutic problems arise.

All too often parents are told by the examining physician that they should "forget" about a hemangioma and that "it will go away," without the information that the going away may take years and that, forget it or not, these vascular tumors bear watching. A "let's wait and see" approach is acceptable if the lesion is quiescent or is one in which the previously red center is turning bluish-white, for then spontaneous involution may be taking place. The physician should keep observing these growths, however, and be ready to initiate therapy if conditions warrant.

The proximity to other tissues and influences thereon should be noted. For example, deep lesions about bone may stimulate osseous growth. Lesions along the distribution of the fifth cranial nerve may have vascular lesions in addition, located in the skull or brain, and calcifications may be a part of these tumors at the latter sites. Increased intraocular tension may be associated with a nevus flammeus located on the same side of the face.[3] The premature infant, in addition to having a high incidence of retrolental fibroplasia, frequently has multiple hemangiomas on the skin.[2]

Hemangiomas may break down, bleed or become infected either with or without apparent trauma. When they are present on exposed parts of the body, the problem may be a social one as well as medical. Internally, these growths can affect any organ, the liver being prone to tumors of this type. Symptoms referable to internal tumors of the vascular type are usually those of pressure or blood loss.

CASE REPORTS

The following cases serve a dual purpose: they illustrate the three primary types of hemangiomas, and some show the social problems with which they can at times be associated.

CASE I. S.C., a white boy aged 6 years, has had a nevus flammeus (Fig. 53) on the right side of his face since birth. Studies of the eye on the involved side as well as x-ray plates of the skull showed no abnormalities to be present. At the age of 3 years "sandpapering" was done to the affected side with no appreciable improvement. Over the years of observation the mother was questioned repeatedly regarding the child's acceptance of this lesion as well as his adjustment to other children. At all times this was seemingly adequate. However, during the first year of school kleptomania and pugnaciousness appeared to the point that his removal from the first grade was not only requested, but also insisted upon. Subsequent study revealed that much of his antagonism stemmed from the jibes of his fellows referring to the skin markings. This, of course, was only one of the precipitating factors. Complex problems in the family background had played their part for years.

Management is now a dual responsibility of the Department of Dermatology and

the Child Guidance Section of the Children's Memorial Hospital. Locally, thorium-X in an alcoholic solution is to be used. Study and care from the psychiatrist, psychologist and social workers must continue for an extended period with service to the parents as well as the child.

CASE II. F.D., a female infant aged 3 months, has a nevus vasculosus (strawberry mark), located on the left side of her chest (Fig. 54). The mother stated that at birth the skin in the involved area was normal in appearance, but that at the age of 2 weeks a tiny red dot became visible. Within a period of 5 weeks a tumor 2 cm. in diameter

Fig. 53. Nevus flammeus type of hemangioma.

Fig. 54. Nevus vasculosus (strawberry mark) adjacent to the left breast.

and elevated 0.5 cm. above the level of the skin was present. At this time the child came to our attention. Because of maternal inadequacies this child was removed from her mother's care and influence, becoming a ward of the courts. Eventually adoption elsewhere was permitted. Social agencies usually desire correctible defects rectified prior to the new parents' assumption of care and responsibility, and so the tumor received 5 treatments with dry ice at regular intervals, resulting in a cure. In deference to the proximity of the breast the use of x-ray therapy was excluded. How much simpler it would have been to obliterate the first tiny signs of this lesion with a single short exposure to cold therapy!

CASE III. N.J., a female infant aged 7 months, has a cavernous hemangioma located on the left side of the head in the area of the mastoid bone (Fig. 55). At birth the

child had a tiny red dot located at the site of the present tumor mass. Suddenly at the age of 2 months rapid growth ensued, resulting in a mass 4 cm. in diameter and several centimeters thick. On palpation the underlying bone was depressed. Excision by the surgeon resulted in an excellent cosmetic result.

Much parental concern and possibly the extensive mass could have been held within bounds by closer observation and earlier intervention.

DIFFERENTIAL DIAGNOSIS

Acquired vascular dilatations can occur either as a local process or as the result of some general disturbance affecting pre-existing blood vessels.

The *nevus araneus*, or "spider nevus," is frequently seen on the face, but can be found on any location of the skin. It consists of a central,

Fig. 55. Cavernous hemangioma with central capillary type of hemangioma.

bright red, elevated blood vessel with fine radiating branches. This is a small arteriovenous anastomosis. In older persons similarly appearing pulsating angiomas can appear as part of liver disease or during pregnancy. Familial tendencies for the appearance of telangiectasia associated with a frequency of bleeding from the nose or hemorrhage elsewhere from the body constitute the Rendu-Osler-Weber disease. As a result of such bleeding a severe degree of anemia may be present. Infrequently the *venous varix*, a simple cystic dilatation of a vein, may occur.

The *cirsoid aneurysm*, also known as the racemose type of hemangioma, is primarily a congenital arteriovenous fistula. These pulsating vascular tumors are usually in the area of the carotid artery and consist of a tangle of vessels capable of extension to the point of bone erosion.

The rapid appearance of a red pedunculated nodule on the skin, usually at the site of previous trauma, suggests a *granuloma pyogenicum* (Fig. 56). This tumor is friable, bleeding easily. On removal and examination under the microscope the finding of a nodule of new capillaries

with a pedicle type of dermal attachment and an infiltrate compatible with a subacute state of inflammation confirms the clinical impression.

The presence of translucent vesicles along with a "cayenne pepper"-appearing tiny angiomatous studded surface is indicative of a *lymphangioma.* Soft compressible masses having the appearance of normal skin

Fig. 56. Granuloma pyogenicum located on thigh.

Fig. 57. Lymphangioma of left cheek.

are variations of this (Fig. 57). When projecting from the axillary or supraclavicular area, they may constitute the *cystic hygroma.*

A most infrequent eruption is that of *angioma serpiginosum* (Fig. 58). In this condition angiomatous puncta may be seen in patches having varied configurations. Involution, either with or without therapy, is usually slow, spontaneous and incomplete.

Malignancies originating from blood vessels occur infrequently in the infant. The two types of malignancies of blood vessels are the *hemangiosarcoma* (*fibrosarcoma*) and the *hemangioendothelioma*. The clinical picture of lesions of the latter type usually is not specific, consisting of dark red vascular masses having invasive and metastasizing ability, frequently bleeding and ulcerating. Microscopic studies of such tissue reveal the presence of classic features of malignancy. The former type, the hemangiosarcoma, is usually found in older persons.

Fig. 58. Angioma serpiginosum located about the knee in a 10 year old boy.

TREATMENT

The treatment of vascular tumors is individualized to the type of the presenting lesion. The more commonly used methods include freezing, radiotherapy, injection of various sclerosing materials and surgical resection. On occasion one may have to use more than one technique before the desired result is obtained.

Nevus Flammeus

The problem of the nevus flammeus type of lesion is great. Many types of treatment have been tried with varying degrees of success. Many cases have shown improvement after vigorous application of sandpaper to the anesthetized area with the usual attention given to basic surgical principles of care. Others report good results after the use of grenz-ray therapy, thorium-X therapy, tattooing or camouflaging with cosmetics.

At this time we prefer to treat these patients with *thorium*-X.[5] This

material is obtained in a solution of isopropyl alcohol having a predominance of alpha radiation with only a small quantity of beta and gamma activity present.

The patient is prepared by careful cleansing of the area to be treated with a degreasing solution such as acetone. Then the border of the lesion is ringed with petrolatum. This is a precaution taken to prevent the solution from getting on normal adjacent skin and inducing pigmentation. A cotton-tipped applicator is dipped into the alcoholic solution of thorium-X and then rubbed over the area to be treated. In a short time the alcohol evaporates, leaving the treated area dry. Again the thorium-X is applied and drying allowed to ensue. After the third application the area is coated with flexible collodion, and the patient retains this film for about four days. By this time the previously applied medicine has lost its therapeutic activity and is inert. Usually this film has been removed by the patient. If it is still adherent, the physician may remove it with a little acetone.

Thorium-X is obtainable in various concentrations measured in electrostatic units or microcuric units per cubic centimeter. The weaker concentrations are used to initiate therapy, and repeat treatment may be done at five to six week intervals. By the eighth to the tenth treatment one should be able to evaluate its worth. As with all therapeutic procedures about the head, one should exclude the presence of other lesions especially as related to the eye. Since one is using a radioactive material, the medicolegal implications of such usage should be appreciated.

Tattooing and *surgical intervention* have their advocates. In skilled hands such therapy offers varying degrees of improvement in the nevus flammeus and is worthy of consideration when simpler techniques, including camouflaging with cosmetics, are not satisfactory. At all times one must weigh the defect at hand against the possible resulting defect following therapy.

Nevus Vasculosus

Capillary nevi as found in the nevus vasculosus type of lesion are more amenable to therapy. Too, spontaneous involution occurs frequently. On initiating active therapy one should measure the growth, obtaining width, length and thickness. The color changes are an index to involution. Colored pictures make excellent progress records.

Dry ice is of great use on the "strawberry mark." One can obtain this as a large cake and, by removing pieces as needed, shape the dry ice to the size of the area to be treated, using a piece of firm metal (bandage scissors, or the like) as the shaping agent. While this is being done the operator holds the dry ice in several thicknesses of cleansing tissue to avoid self-injury. The dry ice is then applied to the area to be treated with moderately firm pressure for about four to six seconds. The treated area becomes blanched and hard. The dry ice is then removed. After a few seconds the treated area begins to thaw, color returns, and some degree of discomfort is felt by the patient. After this treatment the area usually becomes blistered and over a period of seven to ten days heals. Treatment may be repeated every three weeks until the desired result is obtained. One can protect the surrounding normal skin by making a

pattern of the area to be treated on heavy paper, cutting it out and fitting it to the lesion and then applying the dry ice to the exposed tissue. If the dry ice is not available, one may procure "snow" from either the large carbon dioxide tanks or the small portable units and through the use of molds make various-sized sticks of dry ice for therapy.

Infrequently, an area treated with dry ice becomes secondarily infected. Further therapy with this technique must await the clearing of the infection and the complete healing of the skin. Skin changes objectionable from a cosmetic standpoint may result at the treated site, but with the passing of time most treated areas become practically invisible.

Radiation therapy does well in many of these lesions. This may be administered as a radioactive plaque, needles or by the x-ray machine, the choice influenced by individual preference. The radiation initiates a response eventuating in a sclerosis and a fibrosis of the tumor mass. In principle, one gives doses well within the range of the amount required to redden the skin. Repeat treatments are weeks to months apart. Total dosage is always well within the limits of skin tolerance, for the gauge of response is not the immediate result, but what the treated area will look like ten to 20 years hence.

One must evaluate the site of the vascular tumor. The presence of an epiphysis, open fontanel, proximity to the eye, the possibility of inducing sclerosis of an orifice, the effect on special tissues, such as the breast, should be weighed before radiation becomes the treatment of choice. Radioactivity alters normal biologic, biochemical and physical behavior of the exposed tissue. Excess use induces permanent cellular damage. The immediate results of excess local exposure include erythema, vesiculation, desquamation, an indurated type of edema, and necrosis. Late effects which can occur months to years after exposure include hyperpigmentation or depigmentation, telangiectasia, wrinkles, atrophy, ulcers and scars. New growths may arise on the injured sites showing changes ranging from premalignant states to absolute malignancy. The stunting of a growth center or loss of a bud prohibiting breast development is a harsh price to pay for injudicious therapy on a benign lesion. One must exercise great care and judgment when using radiation therapy.

The injection of various *sclerosing substances* works well in nevus vasculosus. The technique and material used are the same as in the treatment of varicosities. Injections are administered weekly. These are usually associated with some pain and discomfort. The involution of the tumor seems to be slower than when dry ice is used.

Cavernous Hemangioma

Many tumors that are seen in the cavernous category as well as those nevus vasculosus lesions in areas where other techniques are contraindi-

cated are best treated by the surgeon. In the circumscribed type of lesion the removal is not too difficult when one is able to clear, isolate and tie off the vessels entering and leaving the tumor. The task is well nigh impossible for removal of the total lesion when one has to deal with the diffuse ramifying type in which vessels extend deeply, widely and without restriction. Interstitial radiation is frequently used on growths of the cavernous type, success varying with the sensitivity of the tumor.

CONCLUSION

Hemangiomas should not be ignored because of their usual cycle of growth leading to spontaneous involution. When conservative management is the treatment, the lesion should be evaluated at frequent intervals.

The technique used in treatment is dependent on the anatomic type of the presenting lesion with earlier intervention offering some hope of prevention of future medical and social problems.

The choice of therapy is influenced by location as well as type of the vascular tumor.

REFERENCES

1. Andrews, G. C.: Treatment of Angioma. Arch. Dermat. & Syph., *37*:573, 1938.
2. Andrews, G. C., and Domonkos, A. N.: Skin Hemangioma and Retrolental Fibroplasia. Arch. Dermat. & Syph., *68*:320, 1953.
3. Green, J. R., Foster, J., and Berens, D. L.: Encephalotrigeminal Angiomatosis. Am. J. Roentgenol., *64*:391, 1950.
4. Lister, W. A.: The Natural History of Strawberry Nevi. Lancet, *1*:1429, 1938.
5. Nagelschmidt, K. F.: External and Internal Thorium-X Therapy. Brit. J. Radiol., *19*:31, 1946.
6. Ribbert, V. A.: Ueber Bau, Wachsthum und Genese der Angiome, nebst Bemerkungen über Cystenbildung. Arch. f. path. Anat., *151*:381, 1898.
7. Van der Werf, E.: Spontaneous Disappearance of Hemangiomas. Nederl. tijdschr. geneesk., *98*:676, 1954.

25 East Washington Street
Chicago 2, Illinois

AMBLYOPIA EX ANOPSIA

A Preventable Form of Blindness

TRYGVE GUNDERSEN, M.D.

Amblyopia ex anopsia ranks second to none as a preventable cause of blindness and should, therefore, be thoroughly understood by all pediatricians as well as by all general practitioners.

INCIDENCE

Recent statistical studies have clearly demonstrated its high incidence. In 1945 Downing[1] reported an incidence of amblyopia of 1.02 per cent among 1920 selectees. It is important that somewhat less than half of these (44 per cent) had neither convergent nor divergent strabismus. Glover and Brewer,[2] in reviewing more than 20,000 men at the Altoona Induction Center at Altoona, Pennsylvania, found that 2.27 per cent of the inductees examined had congenital amblyopia, with vision of 20/70 or less in one eye. With these figures in mind it seems reasonable to assume that the number of persons in this country with uniocular blindness due to amblyopia ex anopsia may well be over one million.

The blindness of amblyopia ex anopsia concerns only one eye, and persons so afflicted generally live out their lives with no great handicap, never knowing blindness in the usual sense. Yet, what ophthalmologist has not seen the tragedy of injury in early life or disease in later life strike the only good eye of the amblyopic person? He is therefore forced to enter this patient's name, all too prematurely, on the rolls of the legally blind. Consider also the lifelong handicap of the monocular person. In our industrial age many able-bodied men and women are being denied employment for this reason alone.

Prevention of amblyopia ex anopsia may be simply a matter of its early detection by visual acuity determination.

Most physicians know that amblyopia ex anopsia frequently accompanies strabismus. Fortunate is the child whose physician knows this and refers him to an ophthalmologist as soon as the strabismus is detected. Many children, however, do not benefit from such knowledge. The familiar story is too often given us: "Our doctor told us that there is no hurry about the operation," or, "We were told that our child might outgrow the squint." Catastrophe following such unenlightened advice is all too frequent.

In many other children no visible evidence of strabismus exists. Few physicians other than ophthalmologists appreciate the fact that uniocular blindess may be equally intense in children with refractive amblyopias, in children whose convergence is so slight as to escape notice, or in children with no deviation of the visual axes whatever. Our only hope of combating uniocular blindness in this group is by testing the visual acuity of *all* children at the earliest possible moment.

VISUAL ACUITY DETERMINATION

A visual acuity determination can be done on any normal child on his third birthday. The third birthday may be looked on as a large milestone in a child's development. Within a few months of this date an average child suddenly becomes more docile, begins to submit to reason, usually becomes "house-trained" and will cooperate sufficiently so that one eye may be covered and the vision of the opposite eye measured.

The earliest visual acuity test can be made by the use of picture cards. The Osterberg Test Charts (Nyrop and Maag a/s, Copenhagen, Denmark) are of especially good design and most useful.* Similar picture cards, though less modern and less well designed, can be obtained in this country. These cards must have six to eight pictures of different objects which a three year old child can easily recognize. Pictures of a house, man, horse, car, scissors, Christmas tree or even a well drawn airplane are most readily recognized. These pictures are, of course, drawn to scale according to the Snellen notation.

Several points about testing the visual acuity of a three year old child should be emphasized. Obviously a friendly atmosphere is paramount. The child should be told that it is a game rather than an examination. A quiet room without distraction is best, and no one save child, mother and examiner should be present. A tired, frightened or fretful child makes examination impossible, and another date for examination may as well be chosen at the outset. The examiner must bear in mind that a three year old's attention span is often momentary or, at best, of only

* The illiterate E chart or, better still, the Sjogren Hand can be used only a year later, on the child's fourth birthday.

a few minutes' duration; so the examination must be made rapidly with as many short-cuts as possible.

Technique

First the chart should be presented to the child at the ordinary reading distance, and each picture should be pointed out so that the child will name them successively. Thereafter the chart is moved off to a distance of not over 12 feet, since it is difficult to hold a child's attention at a greater distance. At this point the child is best seated on his mother's lap, and while the examiner starts by pointing to large pictures on the chart, the mother slowly places the palm of her hand over the child's left or right eye. A child usually will accept this occlusion unless by chance, in the case of amblyopia, the mother has covered the good eye. If this has happened, the child will resent the occlusion and struggle against it. In this situation the other eye should be examined first. As smaller and smaller pictures are pointed out, it soon becomes obvious whether or not the visual acuity is equal in both eyes and whether or not it is normal. Remember that one can never obtain visual acuity determinations on a three year old child comparable to those which one can obtain on an older one. Roughly speaking, the three year old child will recognize and name pictures 1.5 to 2 cm. in diameter with each eye separately at 12 feet. This is comparable to 12/30 or 12/40 in the Snellen notation.

CONCLUSION

By this simple method and with no other equipment than a good Snellen picture chart, the visual acuity of a three year old child can quickly and easily be determined. When a difference in acuity between the two eyes is found, competent ophthalmologic advice should be sought, and in the case of the amblyope forceful occlusion should be instituted immediately. In no other way can the high incidence of amblyopia ex anopsia existent in this country today be materially reduced.

REFERENCES

1. Downing, A. H.: Ocular Defects in 60,000 Selectees. Arch. Ophth., 33:137, 1945.
2. Glover, L. P., and Brewer, W. R.: Ophthalmologic Review of More than 20,000 Men at Altoona Induction Center. Am. J. Ophth., 27:346, 1944.

101 Bay State Road
Boston 15, Massachusetts

SUPPLEMENT TO ANNUAL STATEMENT ON POLIOMYELITIS

The trivalent, formalinized vaccine against poliomyelitis, developed by Dr. Jonas Salk, is safe *and* highly effective in preventing paralytic poliomyelitis under natural conditions of exposure to the disease.

These facts were confirmed by the report of the 1954 field trials of the vaccine, issued by Dr. Thomas Francis, Jr., director of the independent Poliomyelitis Vaccine Evaluation Center. In essence, Dr. Francis stated that the vaccine was 80 to 90 per cent effective in preventing paralytic poliomyelitis.

Dr. Salk recommended a two-dose primary immunization schedule against poliomyelitis. On the recommendation of its Vaccine Advisory Committee, the National Foundation for Infantile Paralysis has decided to follow Dr. Salk's recommendation. The current (1955) dosage schedule for the Salk vaccine is therefore as follows:

Two doses of 1 cc. each administered two to four weeks apart.

A third or "booster" dose given no sooner than seven months thereafter.

HIGHLIGHTS OF THE FRANCIS REPORT

The Francis study evaluated the differences in the incidence of poliomyelitis among vaccinated and unvaccinated (control) children during the second half of 1954. The study was arranged in four stages of analysis which sought progressively to eliminate those cases which might be considered less conclusively established as poliomyelitis. Through these four stages there appeared a progressive increase in the percentage effectiveness of the vaccine. The more certainly diagnoses of poliomyelitis were confirmed or disproved, the more evident it became that the vaccine was effectively preventing paralytic poliomyelitis. This analysis was done separately for the observed control and the placebo control groups. More confidence was placed in the placebo studies.

The crudest data comprised the total cases reported. When the obviously nonpoliomyelitis cases and nonparalytic poliomyelitis cases were eliminated, because these latter showed no significant difference between vaccinated and control cases, the vaccine appeared to be 72 per cent effective in placebo areas and 62 per cent effective in observed control areas.

A second stage of the analysis separated spinal paralytic and bulbospinal cases, in which clinical diagnosis is highly definite and virus recovery higher. In placebo areas the vaccine appeared up to 60 per cent effective against spinal paralysis and 81 to 94 per cent effective against bulbospinal paralysis. When spinal and bulbospinal cases confirmed by laboratory study were considered—a third refinement of data—the vaccine appeared up to 91 per cent effective in preventing the bulbospinal disease and up to 82 per cent effective in preventing spinal paralytic cases.

The fourth step related to cases from which a specifically identified type of virus was recovered. In placebo areas the vaccine proved highly effective against types II (100 per cent) and III (92 per cent) viruses, and somewhat less effective (68 per cent) against type I. The failure of higher protection

against type I has been ascribed to the presence of a preservative which, in some lots of vaccine, lowered the antigenicity against type I.

In summary, *the Salk vaccine may be said to be 80 to 90 per cent effective against paralytic poliomyelitis.*

RATIONALE AND RESULTS OF THE TWO-DOSE SCHEDULE

Dr. Salk's studies have demonstrated that the first two inoculations in a three-inoculation series are sufficient to produce primary stimulation of antibody in the blood serum. Over a period of months a hyper-reactive state develops. During this period the level of antibody may not be high. However, when a "booster" dose is given at least seven months later, the antibody level rises quickly. Most significantly, once the hyper-reactive stage is reached, a natural poliomyelitis infection will also induce rapid, high-level production of antibodies. This is like adding a "live-virus" vaccine for the third inoculation.

Dr. Salk is of the opinion that the 1954 field trials affirmatively answered the question whether *primary* vaccination alone (achieved with a three-dose schedule in which the third dose was given only five weeks after the first) was effective in preventing paralytic poliomyelitis. He strongly feels that if the third dose is delayed much longer, about seven months, *full* immunization can be achieved and that this will persist for a much longer time at higher levels of measurable antibody protection. The goal of poliomyelitis vaccine protection can therefore be considered to be full immunization.

The National Foundation had contracted for sufficient vaccine on a three-dose schedule to permit vaccination of all the approximately 9,000,000 first and second grade children in the United States with vaccine supplied by the Foundation. This program, under the direction of state public health officers, remains in effect. However, the Foundation has turned back into the pool of vaccine available for distribution through commercial channels the vaccine saved in the two-dose schedule. This will permit inoculation of 4,500,000 additional persons with primary immunizing doses before the 1955 poliomyelitis season.

With the better vaccine now available it is probable that the two-dose immunization will give better primary immunization than the five-week three-dose schedule used last year.

Hart E. Van Riper, M.D.
Kenneth S. Landauer, M.D.
The National Foundation for Infantile Paralysis

POLIOMYELITIS, 1955

HART E. VAN RIPER, M.D.

KENNETH S. LANDAUER, M.D.

The year 1955 marks a turning point in the direction of attack on the problems of poliomyelitis. Just two years ago in a Symposium on Poliomyelitis 1953* the editor of the symposium, Dr. Waldo E. Nelson, wrote in his Foreword: "Unfortunately a vaccine for other than investigational purposes cannot be expected within the near future."

This observation was fully justified at the time it was written. Today, however, in the spring of 1955, a poliomyelitis vaccine which would make possible the initiation of a widespread, if not universal, program of vaccination against paralytic poliomyelitis appears to be at hand.

Almost unprecedented progress in the development of a vaccine has taken place in the last two years. It is not to be inferred that the vaccines now developed represent the last word and final direction of research in the prevention of paralytic poliomyelitis. Nevertheless the trivalent, formalinized poliomyelitis vaccine developed by Dr. Jonas Salk of the University of Pittsburgh gives strong substance to the hope that the vast reduction, if not elimination, of new cases of paralytic poliomyelitis lies in the near rather than the distant future.

At the same time it must be recognized that, at least for a few years to come, cases of paralytic poliomyelitis will occur and that many of these will come under the care of pediatricians. These patients should certainly have the benefit of the advances in the treatment of acute and postacute poliomyelitis that have accumulated in recent years. In particular they should have the benefit of the medical team approach to their peculiar problems. Those requiring mechanical aids for breathing to save their

From the National Foundation for Infantile Paralysis, New York City.

* Waldo E. Nelson, ed.: Symposium on Poliomyelitis 1953. P. CLIN. NORTH AMERICA, Vol. 1, number 1A, 1953, p. iv.

lives should be managed so that they do not become utterly dependent on—"addicted to," one pediatrician suggests—tank respirators.

Significant new information on the management of poliomyelitis patients with respiratory difficulties has been developed at 13 respiratory centers established in the United States since 1950 with the support of the National Foundation for Infantile Paralysis.

In addition to whatever new cases of paralytic poliomyelitis may occur, it is estimated that there are at least 35,000 persons seriously disabled by poliomyelitis in the United States who still need further intensive rehabilitation.

In prospect, then, are the hopes of preventing paralytic poliomyelitis through a widespread program of vaccination, of managing more effectively whatever new cases occur and of reducing the handicaps of many patients who contracted the disease in earlier years.

POLIOMYELITIS VACCINE

Background of 1955 Vaccination Program

Plans for a nationwide vaccination program against poliomyelitis in the spring of 1955 had to be made *before* it could be known whether the vaccine developed by Salk was effective—and *how* effective—in preventing paralytic poliomyelitis under natural exposure to the disease.

Constructive advance planning had to be done on the *assumption* that the vaccine was significantly effective, but with full recognition that the plans would have to be modified or discarded if this did not turn out to be the case. Many groups and individuals participated in this planning.

To provide an exact picture of the 1955 plans and hopes it is worthwhile to review briefly the background of research in poliomyelitis which led to the development of a vaccine by Dr. Salk, to its wide-scale field testing in 1954, and to the evaluation of the field trial and the vaccine by the independent Poliomyelitis Vaccine Evaluation Center at the University of Michigan under the direction of Dr. Thomas Francis, Jr.

The suggestion that a vaccine or serum might be used to prevent paralytic poliomyelitis dates back almost half a century—almost to the time of the first demonstration by Landsteiner in 1909 that poliomyelitis is a virus disease and could be experimentally transmitted to monkeys. Flexner and Lewis presented the possibilities of active immunization and passive serum protection against experimental poliomyelitis in 1910.

However, a great deal of factual information about poliomyelitis had to be developed before a program of active or passive immunization against the disease and its paralytic manifestations could become hopeful and practical. An important part of the total research program was the gradual demonstration that poliomyelitis is not a "mystery disease," unique in all its manifestations, but that it can be brought within the laws and principles of immunology common to other infections and communicable diseases. Many investigators helped establish this fact.

Some of the earlier investigators were hampered by lack of methods suitable to the problem they were investigating. In a comprehensive review of immunization against poliomyelitis, up to 1953, Boyd pointed out the most serious sources of earlier errors: for example, lack of quantitative methods for assaying virus and antiserums, unfamiliarity with immunologic differences between virus types, and use of inappropriate animal species and routes of administration for testing resistance to infection conferred by immunizing procedures. Owing to the lack of fundamental knowledge about poliomyelitis, earlier attempts to provide products for the immunization of human beings against paralytic poliomyelitis failed.

New lines of research which began to develop rapidly just five or six years ago quickly opened new doors to the evolution of practical programs of immunization against paralytic poliomyelitis. It had long been suspected that there was more than one type of poliomyelitis virus among the many strains encountered. In the hope of bringing some order out of the chaos, a committee on virus typing, supported by the National Foundation for Infantile Paralysis, began in 1949 a virus-typing program which clearly demonstrated by 1951 that there are just three immunologic types of virus (Types I, II and III) among hundreds of strains of virus tested. There remains the theoretical possibility that a fourth type of poliomyelitis virus exists, but conscientious research to date has not been able to demonstrate it.

A group of minor illnesses simulating nonparalytic poliomyelitis was discovered to be caused by the newly identified Coxsackie group of virus—so named from the town in New York state where these viruses were first discovered. In one study area, reported by Walton and Melnick,* Coxsackie virus accounted for about one quarter of all the illnesses with fever and sore throat occurring among children under ten during the month of August.

Tissue culture studies proved to be the powerful new weapon of research in poliomyelitis. In 1949 Enders, Weller and Robbins demonstrated that poliomyelitis virus can be grown in tissue culture on nonnervous tissue. They received the 1954 Nobel prize in medicine and physiology for this and related discoveries.

Tissue culture technique opened the way to new research endeavors in poliomyelitis in several ways. It broke a "bottleneck" of dependence on expensive and not always available monkeys. Because it permitted comparatively inexpensive and rapid virus isolation and neutralization studies of poliomyelitis viruses, it set the stage for wide-scale epidemiologic investigations of the disease. Further, it provided a practical means for the large-scale production of virus vaccines.

Other lines of research also provided rationale for protection against paralytic poliomyelitis by means of active or passive immunity. In 1952 Bodian and Horstmann independently demonstrated that a stage of

* Walton, M., and Melnick, J. L.: Coxsackie Virus Antibody and Incidence of Minor Illness during the Summer. Pub. Health Rep., 68:12, 1167, 1953.

viremia occurs in the course of poliomyelitis infection. This strongly suggested that poliomyelitis antibodies circulating in the blood might have a good chance of preventing poliomyelitis virus from invading and damaging the central nervous system.

Shortly thereafter, in field trials with gamma globulin which supplied a degree of temporary passive immunization, Hammon showed that even barely detectable levels of circulating antibodies offer temporary protection against paralytic poliomyelitis. Howe and Morgan demonstrated that an inactivated virus vaccine, invoking active immunization, raises antibody levels.

The work of these and other investigators encouraged and bulwarked Salk's efforts to produce a safe, potent and practical vaccine against poliomyelitis, a direction of research that he began following in 1951.

The Vaccine Developed by Salk

The essential facts concerning the manufacture of the poliomyelitis vaccine developed by Salk are these: Bulk tissue cultures are prepared with minced monkey kidney as the cell substance and a complex synthetic nutrient fluid added. The cultures are seeded with a strain of each of the three known immunogenic types of poliomyelitis virus. Each type is grown separately. The virus is harvested after an optimum growing time and inactivated by exposure to a 1:4000 solution of U.S.P. formaldehyde to the point where no measurable amount of virus activity remains. The formaldehyde is then neutralized with sodium bisulfite. The three vaccines are then pooled into a single trivalent vaccine, ready for packaging and labeling after testing each lot and batch for safety and antigenicity.

An elaborate protocol has been established for the safety-testing and antigenicity-testing of the vaccine. In fact, it requires about three months to manufacture and test each lot of vaccine. This circumstance, as much as any other, necessitated elaborate advance planning in order to assure the availability of vaccine for possible use in 1955, should it prove effective.

It can certainly be said categorically that *the trivalent, formalinized vaccine developed by Salk is safe*. This was demonstrated in clinical trials with the vaccine conducted by Salk in the Pittsburgh area before a nationwide field trial of the vaccine was begun on April 26, 1954. During the trial approximately 440,000 school children received three 1-cc. doses of the vaccine. There was an absolute minimum of adverse reactions to the vaccine. Allergic skin reactions appeared in a very few children. These reactions were attributable to the traces of penicillin included during manufacture to preserve the vaccine from bacterial contamination.

The 1954 poliomyelitis vaccine field trial was the largest controlled experiment of its kind in medical history. The trial was conducted in 217 test areas in 44 states in the United States where, in addition to the 440,000 children who received vaccine injections, 220,000 received

placebo injections. Approximately 40,000 children gave a total of about 110,000 blood samples. A total of about 1,830,000 children and their families in the test areas remained under continuous observation for the test year. Careful follow-ups were made of every reported case of poliomyelitis in the test group. These follow-ups included obtaining blood and stool samples in order to help establish the diagnosis.

All reported cases were visited by specially instructed physical therapists, under the direction of physicians, ten to 20 days and again 50 to 70 days after onset of the reported disease in order to score the degree of muscle paralysis, if any.

The data obtained from this field trial, sponsored by the National Foundation, were accumulated, verified and interpreted at the Poliomyelitis Vaccine Evaluation Center under Dr. Francis. The scrupulous and comprehensive planning for the trial and the meticulous search for all pertinent data give an exceptionally high degree of validity and reliability to the results reported by Dr. Francis and his associates.

It should be remembered that two distinct studies were involved in the evaluation of the 1954 field trial. One study concerned the test areas where only second grade children received vaccine injections, while first grade and third grade children served as "observed controls." The second study dealt with "placebo control" areas, where half the children in each of the first three grades received vaccine and half received placebo.

The possibility of having a large quantity of vaccine in 1955 for use against poliomyelitis arose from a decision taken by the National Foundation in the fall of 1954—even before the follow-up period of the field trial was completed and long before an evaluation of its results could be expected. This decision was to take a calculated financial risk and place contracts with six pharmaceutical manufacturers to make enough vaccine to vaccinate 9,000,000 children before the summer of 1955, should the vaccine be found effective. These contracts also enabled the manufacturers to keep their production lines going so that a supply of vaccine in excess of that purchased by the National Foundation might be available in the spring of 1955.

Basic policies for a 1955 poliomyelitis vaccine program were formulated and finally agreed on at a meeting held on January 10, 1955, in New York City. Attending the meeting were official representatives of the American Medical Association, the American Academy of Pediatrics, the Association of State and Territorial Health Officers, the U.S. Department of Health, Education and Welfare, the American Public Health Association and the National Foundation for Infantile Paralysis.

The policies were formulated on the *assumption* that the available vaccine manufactured according to the Salk protocols would be licensed for use as "safe, pure and potent" by the Laboratory of Biologics Control of the National Institutes of Health, which has the legal responsibility for licensing biologic products. It was also recognized that the re-

port made by Dr. Francis on the 1954 field trial would be crucial evidence in determining whether or not the product should be licensed.

The gist of the policies agreed on was this: If licensed, the National Foundation would supply the vaccine it had contracted to purchase to state health officers, without charge, in amounts sufficient to provide for the vaccination of two groups of children: (1) children enrolled in the first through the fourth grades of schools which participated in the 1954 vaccine field trials, but who did *not* receive vaccine at the time; and (2) all children enrolled in the first and second primary grades of all public, private and parochial schools in the continental United States, Alaska and Hawaii in the spring of 1955.

The plan of administration of the National-Foundation-supplied vaccine in any state was made the administrative responsibility of the state health officer, as developed in cooperation with the state medical society and state education officials. It was left to the state health officer to designate local health officers, or other qualified physicians, to make arrangements for the administration of the poliomyelitis vaccine in their own communities. Since approximately 20,000 physicians in the United States cooperated wholeheartedly in the 1954 vaccine field trials, it was expected that similar cooperation would be forthcoming in a 1955 vaccine program.

It was recommended that the vaccine for use in 1955 be administered on the same dosage schedule as was used in 1954: namely, 1 cc. of vaccine in each of three doses, given intramuscularly, the second inoculation one week after the first and the third inoculation four weeks after the second. It was recognized that this was not necessarily the optimum dosage schedule and that additional research might suggest others. The crucial factor here, however, is that a certain amount of time must elapse between doses and that the last or "booster" injection usually is the one that brings about a significantly measurable rise in the antibody titer. It is also highly probable that naturally acquired infection with poliomyelitis virus after inoculation with the vaccine may serve as a booster dose and bring about an increase in antibody levels.

Vaccination with the vaccine supplied by the National Foundation is voluntary, and it was always understood that it would be offered only to children whose parents requested it.

Even before the January meeting the National Foundation had announced that once its supply of vaccine had been distributed to state health officers it would be "out of the vaccine business." The supply of poliomyelitis vaccine on the market is obtainable by physicians through normal channels of distribution of biological products.

There was never any expectation that the vaccine available in 1955 was going to be 100 per cent effective or that it was the final word in poliomyelitis vaccines or programs of protection against paralytic poliomyelitis. From every preliminary indication it offered an immediate opportunity, however, of providing a practical program of immunization

against an often tragic disease whose incidence has been climbing. Much research remains to be done in the prevention of paralytic poliomyelitis. The duration of vaccine effectiveness and the appropriate intervals for booster inoculations, if such are needed, remain to be determined. It is of interest, however, that even before the Francis report nine countries besides the United States were making plans to prepare poliomyelitis vaccines of the Salk type.

In the areas of research on the treatment and after-care of patients who contracted poliomyelitis before a practical program for the prevention of the disease could be put into effect, much remains to be done. We turn now to their problems.

TREATMENT OF PARALYTIC POLIOMYELITIS

The early diagnosis of poliomyelitis, in the absence of weakness or paralysis, still taxes the best clinical judgment. There is as yet no quick and simple laboratory test for the determination of an immediate diagnosis. However, tissue culture examinations of blood and stool specimens can—usually later than clinically useful—confirm the presence of poliomyelitis virus or antibodies. Careful observation of the patient is essential to keep up with the often rapidly changing course of the acute disease, to observe signs and symptoms which indicate the need for life-saving measures such as the application of a mechanical aid to breathing as an early aid rather than a last resort. Lower extremity paralysis is least likely to involve respiratory difficulties. Shoulder area involvement often heralds respiratory muscle paralysis.

Deaths from poliomyelitis occur mostly as the result of respiratory failure due to paralysis of respiratory muscles, airway obstruction and/or involvement of vital centers in the brain stem. It should be noted, however, that the case fatality rate in paralytic poliomyelitis has been significantly reduced because improved methods of combating respiratory failure have been developed and used. The introduction of the first dependable tank-type respirator by Drinker in 1929 was an enormously important step in this direction. However, as clinical experience since then has amply demonstrated, the "iron lung" is by no means the sole answer to the clinical problem of saving the lives of poliomyelitis patients with respiratory difficulties and may tend to create some serious clinical problems of its own.

Frequent measurement of vital capacity is the best guide to early, helpful use of respiratory aids. Impending respiratory failure can be predicted, and early assistance can help avoid further damage from hypoxia. While milder degrees of respiratory muscle weakness can be managed with cuirass respirators or, if swallowing control is intact, on a rocking bed, severe impairment requires a tank-type respirator. The importance of proper adjustment of respirator equipment to avoid either hyperventilation or hypoventilation is better understood today.

Tracheotomies are frequently necessary to maintain an open airway and permit adequate ventilation with or without a respirator. Properly managed, they prevent many emergencies. Positive pressure apparatus attached through the tracheotomy opening facilitates nursing care of respirator patients.

Medical complications that threaten life, particularly pneumonitis and atelectasis, are better handled with the use of antibiotics, mucolytic agents and mechanical devices that help the patient to cough.

For patients whose breathing difficulty persists the technique of glossopharyngeal breathing, dubbed "frog breathing," offers many advantages. These include improvements in voice and cough, greater opportunity for physical therapy programs to increase pulmonary compliance, insurance against failure of mechanical equipment, and greater independence. Most patients who can benefit by glossopharyngeal breathing can be taught the technique in varying periods of time; they learn to use their tongues as pumps and inflate their lungs with air.

Functional muscle improvement is being attained by intensive physical and occupational therapy and by muscle transplant operations as well as by functional bracing and assistive and adaptive devices keyed to improved attention to physical and occupational therapy. The trend is to earlier bracing. Many extremely ingenious devices have been developed for extending the ranges of function of the upper extremities and the hands. It is recognized that even a small degree of muscle function improvement here may enable a patient to do a great many new things for himself and therefore greatly improve his psychologic outlook.

Vital also to many patients is the new outlook toward their rehabilitation. It is suggested to them as early as possible that they are in the hospital to improve and that every effort will be made to get them back home as soon as possible. This encouragement appears to be a powerful incentive in weaning patients from tank respirators to lesser mechanical aids, such as cuirass respirators (chest shells) and rocking beds. Mechanical respiratory aids are constantly being improved.

Grouping of postacute poliomyelitis patients, especially those with respiratory problems, in poliomyelitis units or respiratory centers offers great therapeutic and economic advantages. The patients so located give each other great stimulus toward recovery.

The goal in the treatment of paralytic poliomyelitis is not only to save life, the first consideration, but also to maintain or restore as much bodily function as possible. Psychologic as well as physiologic factors are important. Many worthwhile advances have been made in recent years in the rehabilitation of patients with paralytic poliomyelitis, particularly those who are seriously disabled and those with respiratory paralysis.*

* Affeldt, J. E.: Recent Advances in Treatment of Poliomyelitis. J.A.M.A., *156*:12, 1954. Spencer, W. A.: Treatment of Acute Poliomyelitis. 2nd edition. Springfield, Ill., Charles C Thomas, 1954.

Respiratory Center Progress

The 13 respiratory centers already established in the United States under the aegis and with the support of the National Foundation for Infantile Paralysis have many purposes. They may be regarded primarily as demonstration centers. Their aim is to stimulate the development of and to demonstrate and teach the techniques and procedures which will enable patients with severe respiratory difficulties and associated paralyses resulting from poliomyelitis to return as nearly and as rapidly as possible to normal life.

The management of respiratory paralysis is greatly enhanced by the medical team approach to the problem. This approach underlies the active treatment programs now in operation in the established respiratory centers. The principles may be applied with modifications, in hospitals or communities where comparatively few patients with respiratory paralysis may be expected. Special knowledge of respiratory physiology and skills in managing patients with bulbar and respiratory muscle paralysis are essential. The intelligent use of mechanical respiratory aids demands a well trained team. Indeed, the team approach is essential in providing the total patient-care services necessary to the rehabilitation of the severely disabled person.

Though not subject to strict definition, the medical team includes, in addition to physicians from many specialties, such associate medical personnel as the nurse and her aides, the physical therapist, the occupational therapist, the medical social worker, the clinical psychologist, the vocational guidance counselor and the teacher. Many other people, of course, are included in the total rehabilitation program, particularly the patient's family.

In order to demonstrate total patient care the National-Foundation-sponsored respiratory centers are organized to give this intensive care to a limited number of patients. In a search for better treatment each center conducts clinical investigation and research. Teaching is also a responsibility of the centers; this teaching is both formal and informal, directed toward physicians, medical students and associate medical personnel. The centers further provide field consultations to physicians and hospitals on request. Finally, they provide a place for the development and clinical testing of equipment and devices of value to poliomyelitis patients. Applications for admission of patients to the centers are made by the patients' own physicians to the directors of the centers, who may exercise their own discretion in the selection of patients necessary to fulfill the many purposes of the centers.

SUMMARY

In summary, the year 1955 brings new directions of hope in both the prevention and treatment of poliomyelitis. The things that are being

learned in the struggle to conquer poliomyelitis have great significance in the hope of prevention and especially in the treatment of other diseases. Respiratory centers have demonstrated that some of the most severely damaged persons can be restored to a near-normal life in a home situation. The rapid progress that has been made against poliomyelitis reflects in part the interest of the American public in this disease and their willingness to support research and education to prevent it and to care for patients who have contracted it.

DIRECTORY OF RESPIRATORY CENTERS

University of Michigan
Poliomyelitis Respiratory Center
University Hospital
Ann Arbor, Michigan

Mary MacArthur Memorial
Respiratory Unit
251 Forest Street
Wellesley Hills, Massachusetts
(Boston—unit of Children's Medical Center)

University of Buffalo
Poliomyelitis Respiratory Center
Chronic Disease Research Institute
2183 Main Street
Buffalo, New York

University of Illinois
Poliomyelitis Respiratory Center
Research and Educational Hospitals
Chicago, Illinois

Western Reserve University
Poliomyelitis Respiratory Center
Cleveland City Hospital
Cleveland, Ohio

Baylor University
Southwestern Poliomyelitis Respiratory Center
Jefferson Davis Hospital
Houston, Texas

Rancho Los Amigos Respiratory Center
Rancho Los Amigos Hospital
Hondo, California
(Los Angeles area)

Vanderbilt University
Poliomyelitis Respiratory Center
Vanderbilt University Hospital
Nashville, Tennessee

New York University
Respiratory Care and Rehabilitation Center
Goldwater Memorial Hospital
New York City

The Jack Martin Polio Respiratory Center
Mt. Sinai Hospital
New York City

Creighton University
Poliomyelitis Respiratory Center
Creighton Memorial-St. Joseph's Hospital
Omaha, Nebraska

Poliomyelitis Respiratory Center and Rehabilitation Center
Fairmont Hospital
San Leandro, California
(San Francisco area)

University of Washington
Northwest Poliomyelitis Respiratory Center
King County Hospital (Harborview)
Seattle, Washington

120 Broadway
New York 5, New York

INDEX

(February—May)

Page numbers of symposium and clinic titles are given in **boldface** type.

ABDOMEN, in newborn infant, *May*, 345
massage, for constipation, *May*, 536
pain in, vague, chronic, *May*, **465–481**
etiologic classification, table, *May*, 468
examination of child with, *May*, 467
findings, table, *May*, 473
history in, *May*, 465
incidence of pathology, table, *May*, 470
pathology, table, *May*, 470
pathology related to, table, *May*, 471
relationship to Enterobius vermicularis infection, table, *May*, 471
Abnormalities, congenital, weight gain failure due to, *May*, 569
electroencephalogram in, *Feb.*, 294
Achalasia, vomiting due to, *May*, 490
Acid, acetylsalicylic, for headache, *May*, 601
in leptospirosis, *Feb.*, 97
Addis count, *Feb.*, 198
Addison's disease, syncope due to, *May*, 612
Adenitis, mesenteric, vomiting due to, *May*, 497
Adolescent, menstrual problems, *May*, **539–551.** See also under *Menstrual problems.*
Adrenals, adrenocortical hyperplasia, congenital amenorrhea due to, *May*, 544
adrenocortical insufficiency, vomiting due to, *May*, 494
cortex, test of function, *Feb.*, 218
tumors of, androgen-producing, amenorrhea due to, *May*, 544
breast enlargement due to, *May*, 585
feminizing, breast enlargement due to, *May*, 591
Adrenals, disorders, amenorrhea due to, *May*, 543
insufficiency, acute, and meningococcemia, *May*, 385
medulla, tests of function, *Feb.*, 222
Agammaglobulinemia, *Feb.*, 273
Age, in etiology of vomiting, *May*, 484
weight gain failure due to, *May*, 570
Agranulocytosis. See *Granulocytopenia.*
Albright's syndrome. See *Polyostotic fibrous dysplasia.*
Albumin milk, *May*, 362
Alimentary tract. See *Digestive system.*
Allergic aseptic meningitis, *Feb.*, 53
Allergy, headache due to, *May*, 600
milk, diarrhea, vomiting and colic due to, *May*, **503–511**
diagnosis, *May*, 505
symptoms, *May*, 504, 505
treatment, *May*, 506
weight gain failure due to, *May*, 569
Amblyopia. See *Blindness.*
Amenorrhea, *May*, 541
Amphetamine in epilepsy, *May*, 608
Amphetamine phosphate for obesity, *May*, 564
Amphetamine sulfate for obesity, *May*, 563, 564
Anemia(s), *May*, 428
aplastic, *May*, 436
neonatal, *May*, 432
as indication for bone marrow examination, *Feb.*, 245
classification, *May*, 431
Cooley's, as indication for bone marrow examination, *Feb.*, 253
hemolytic, *May*, 437
acute, *May*, 437
congenital, as indication for bone marrow examination, *Feb.*, 253
familial, congenital, *May*, 432
hereditary, constitutional, *May*, 438
jaundice due to, *May*, 462
neonatal, *May*, 432

Anemia(s), hemolytic, nonspherocytic, congenital, *May*, 432
treatment, *May*, 439
iron deficiency, *May*, 433
treatment, effect of, *May*, 434
megaloblastic, *May*, 435
bone marrow examination in, value, *Feb.*, 254
neonatal, *May*, 431
etiology, *May*, 431
nutritional, *May*, 435
as indication for bone marrow examination, *Feb.*, 252
of infancy and early childhood, *May*, 433
physical and laboratory examinations, *May*, 429
red cell, pure, *May*, 437
sickle cell, as indication for bone marrow examination, *Feb.*, 253
symptoms, *May*, 429
Anesthesia, for tracheography and bronchography, *Feb.*, 281
vomiting due to, *May*, 501
Aneurysm, cirsoid, *May*, 619
Angioma. See under *Tumors*.
Anomalies. See *Abnormalities* and under specific organs and regions.
Anorexia. See under *Appetite, disorders*.
Antibiotics. See also *Chlortetracycline, Penicillin*, etc.
bacterial resistance to, *Feb.*, 313
bacterial sensitivity to, determination of, evaluation of methods, *Feb.*, 309
indications, *Feb.*, 307
value and clinical application, *Feb.*, **305–316**
interpretation and significance of tests in vivo, *Feb.*, 312
bacterial spectrums, *Feb.*, 307
inhibition of bacteria, criteria, *Feb.*, 311
Antispasmodics for constipation, *May*, 537
Anus. See also *Rectum*.
in newborn infant, *May*, 346
lesions, bleeding from, *May*, 522
stenosis, constipation due to, *May*, 529
Aorta, coarctation, heart murmur in, *May*, 447
Aortic pulmonary artery septal defect, heart murmur in, *May*, 447
Aortic valve, stenosis, heart murmur in, *May*, 447
Aphthae, Bednar's, in newborn, *May*, 342
Appendicitis, vomiting due to, *May*, 496
Appetite, disorders, anorexia in coccidioidomycosis, *Feb.*, 114
Ascarids, dog and cat, visceral larva migrans due to infection with, *Feb.*, **163–168**. See also *Visceral larva migrans*.
Aseptic meningitis syndrome, acute, *Feb.*, **47–54**
treatment, *Feb.*, 54
Aspirin. See *Acid, acetylsalicylic*.
Atrial septum, defect of, heart murmur in, *May*, 446
Aureomycin. See *Chlortetracycline*.
Auscultation method of blood pressure measurements, *Feb.*, 259

Backache in coccidioidomycosis, *Feb.*, 114
Bacteria, antibiotic hiatuses, spectrum of, *Feb.*, 314
antibiotic-sensitive, spectrum of, *Feb.*, 308
inhibition by antibiotics, criteria, *Feb.*, 311
resistance to antibiotics, *Feb.*, 313
sensitivity to antibiotics, determination of, evaluation of methods, *Feb.*, 309
indications, *Feb.*, 307
value and clinical application, *Feb.*, **305–316**
interpretation and significance of tests in vivo, *Feb.*, 312
Bednar's aphthae in newborn, *May*, 342
Behavior, disorders, electroencephalogram in, *Feb.*, 302
problems, headache due to, *May*, 599
Benzedrine. See *Amphetamine*.
Benzedrine Sulfate. See *Amphetamine sulfate*.
Beriberi, edema due to, *May*, 396
Bile, concentration, as test of pancreatic function, *Feb.*, 206
inspissated, due to erythroblastosis fetalis, *May*, 458
Bile ducts, atresia, jaundice due to, *May*, 457
Bilirubin, in blood. See *Blood, bilirubin*.
in stool. See *Feces, bilirubin*.
in urine. See *Urine, bilirubin*.
Blindness, amblyopia ex anopsia, *May*, **625–627**
incidence, *May*, 625
Blood, bilirubin, serum levels, average, table, *May*, 451
test of liver function, *Feb.*, 180
cholesterol, serum level, as test of thyroid function, *Feb.*, 217
counts and smears in plague, *Feb.*, 8
examination, in anemias, *May*, 429
in brucellosis, *Feb.*, 81
in plague, *Feb.*, 7
in toxoplasmosis, *Feb.*, 172
fibrinogen, *Feb.*, 272
groups, ABO, incompatibility of, erythroblastosis due to, *May*, 454
incompatibilities, erythroblastosis due to, *May*, 455
Rh factor, incompatibility of, erythroblastosis due to, *May*, 452
in newborn infant, *May*, 348
in stools, *May*, **513–525**. See also *Feces, blood in*.

Blood, pressure, measurements, *Feb.*, **257–263**
interpretations, *Feb.*, 262
normal values, *Feb.*, 261
protein, changes in disease, *Feb.*, 268
fractions, *Feb.*, 272
measurements, in diagnosis of disease, *Feb.*, **265–277**
serum, agglutination test for tularemia, *Feb.*, 14
specimens for smallpox diagnosis, *Feb.*, 24
sugar, hypoglycemia, syncope due to, *May*, 611
tests, in coccidioidomycosis, *Feb.*, 118
in histoplasmosis, *Feb.*, 142
in toxoplasmosis, *Feb.*, 173
urea nitrogen, as test of kidney function, *Feb.*, 194
Blood vessels, great, transposition of, heart murmur in, *May*, 447
Body, fluids, disturbances of, symptoms and signs, *Feb.*, 318, 319
proportions of newborn infant, *May*, 338
weight, gain in, failure of, *May*, 567
in children, *May*, 570
in infancy, *May*, 568
Bone marrow, examination, *Feb.*, **243–256**
in anemias, *May*, 430
in relation to therapy, value of, *Feb.*, 254
indications for, *Feb.*, 245
supportive, indications for, *Feb.*, 251
metastasis as indication for marrow examination, *Feb.*, 248
Bones, maturation of, as test of thyroid function, *Feb.*, 218
Brain, electroencephalography, *Feb.*, **291–303**
abnormal, *Feb.*, 293
changes with age, *Feb.*, 292
in syncope, *May*, 612
normal, in first two decades, *Feb.*, 293
tumors, electroencephalogram in, *Feb.*, 294
Breast, enlargement, *May*, **575–593.** See also *Breast, hypertrophy.*
hypertrophy, associated with endocrine changes, *May*, 580
causes, table, *May*, 575
in male, *May*, 588
physiologic, in adolescent, *May*, 579
in newborn, *May*, 576
pseudohypertrophy, *May*, 592
Breath-holding spells, electroencephalogram in, *Feb.*, 303
Breathing, difficult, *May*, 377
Bromsulfalein excretion test of liver function, *Feb.*, 182
Bronchiolitis, *May*, 378
Bronchogram, *Feb.*, 284
procedure, *Feb.*, 285
Bronchography and tracheography, *Feb.*, **279–289.** See also under *Tracheography.*
Brucella, culture of, *Feb.*, 79
Brucellosis, *Feb.*, **73–85**
clinical aspects, *Feb.*, 78
laboratory diagnosis, *Feb.*, 79
treatment, *Feb.*, 81
Bubo puncture in plague, *Feb.*, 8

Cafergot for headache, *May*, 602
Caffeine for headache, *May*, 602
California disease. See *Coccidioidomycosis.*
Callus, sucking, *May*, 342
Calories, requirements in artificial infant feeding, *May*, 355
Candida infections, *Feb.*, **151–161**
disseminated, *Feb.*, 158
systemic, *Feb.*, 157
treatment, *Feb.*, 159
Canicola fever. See *Leptospirosis.*
Caput succedaneum, *May*, 340
Carbohydrate(s), additions and modifiers, *May*, 366
classification as to physical state and origin, *May*, 366
digestion, theoretical concept, *May*, 367
requirements in artificial infant feeding, *May*, 355
Cardioesophageal spasm. See *Achalasia*
Carotid sinus syncope, *May*, 608
Cat scratch disease, *Feb.*, **33–40**
diagnosis, *Feb.*, 38
laboratory procedures, *Feb.*, 37
treatment, *Feb.*, 38
Cathartics for constipation, *May*, 536
Cavitation in coccidioidomycosis, *Feb.*, 114
Cephalhematoma. See *Cranium, hematoma.*
Cephalin-cholesterol flocculation test of liver function, *Feb.*, 181
Cerebral palsy, electroencephalogram in, *Feb.*, 301
Cerebrospinal fluid, appearance, *Feb.*, 230
bacteriology, *Feb.*, 231
cell count, *Feb.*, 230
chloride content, *Feb.*, 231
examination, *Feb.*, **227–237**
in disease, *Feb.*, 232
in newborn, *Feb.*, 231
in toxoplasmosis, *Feb.*, 172
methods of obtaining, *Feb.*, 229
pressure, *Feb.*, 230
protein content, *Feb.*, 230
sugar content, *Feb.*, 230
values, *Feb.*, 234, 235
Chalasia, vomiting due to, *May*, 490
Chloride in cerebrospinal fluid, *Feb.*, 231
Chlortetracycline, in brucellosis, *Feb.*, 82
in plague, *Feb.*, 9
in psittacosis, *Feb.*, 71
in Q fever, *Feb.*, 68

Cholesterol in blood. See *Blood, cholesterol.*
Choline in leptospirosis complications, *Feb.*, 98
Cirrhosis of liver. See under *Liver.*
Cisternal tap, *Feb.*, 229
Coarctation of aorta. See under *Aorta.*
Coccidioidal granuloma. See *Coccidioidomycosis.*
Coccidioidin skin test, *Feb.*, 116
Coccidioidomycosis, *Feb.*, **109–125**
  clinical picture, *Feb.*, 113
  disseminated, *Feb.*, 115
  laboratory diagnosis, *Feb.*, 116
  treatment, *Feb.*, 121
Codeine in leptospirosis, *Feb.*, 97
Colds, frequent, in young child, *May*, **413–425**
Colic, diarrhea and vomiting due to milk allergy, *May*, **503–511.** See also *Allergy, milk.*
Collagen diseases. *See Fibrinoid diseases.*
Colon, malrotation, vomiting due to, *May*, 492
Constipation, *May*, **527–538**
  causes, classification, table, *May*, 533
  in early childhood, *May*, 530
  in infants, *May*, 528
  psychologic factors in, *May*, 532
  treatment, correction of faulty habits, *May*, 535
    mechanical aids, *May*, 535
    of family, *May*, 533
    of patient, *May*, 534
Constitutional factors, excessive menstruation due to, *May*, 548
Convulsions, *May*, 609
  febrile, electroencephalogram in, *Feb.*, 302
  infantile, *May*, 373
    convulsive work-up, *May*, 375
    differing from acute febrile type, *May*, 374
    febrile, acute, *May*, 373
Cooley's anemia and trait as indications for bone marrow examination, *Feb.*, 253
Corticoid excretion as test of adrenal cortical function, *Feb.*, 220
Cough, as indication for tracheography and bronchography, *Feb.*, 280
  in coccidioidomycosis, *Feb.*, 114
Cough mixtures for frequent colds, *May*, 422
Cowpox, acquired, *Feb.*, 27
Craniotabes, physiologic, *May*, 341
Cranium, hematoma, in newborn, *May*, 341
Creatine excretion as test of thyroid function, *Feb.*, 217
Creatinine clearance test of kidney function, *Feb.*, 193
Curd tension of milk, *May*, 356
Cushing's syndrome, amenorrhea due to, *May*, 544
Cyanosis in congenital cardiac and great vessel malformations, table, *May*, 448
Cyst. See under names of specific organs and regions.

Daraprim. See *Pyrimethamine.*
Death, sudden, *May*, 389
Demerol in leptospirosis, *Feb.*, 97
Developmental factors, amenorrhea due to, *May*, 543
Dexamyl in obesity, *May*, 564
Dexedrine Sulfate. See *Amphetamine sulfate.*
Diagnosis by presenting symptoms, symposium on, *May*, **333–627**
Diaphragm, hernia. See *Hernia, diaphragmatic.*
Diarrhea, bloody, severe, *May*, 514
  vomiting and colic due to milk allergy, *May*, **503–511.** See also *Allergy, milk.*
  with occasional bloody stools, *May*, 519
Diet, in obesity, *May*, 561
  regulation of, in constipation, *May*, 534
  1000-calorie, table, *May*, 562
Dietary indiscretions, vomiting due to, *May*, 500
Dietary intake, weight gain failure in children due to, *May*, 571
  weight gain failure in infancy due to, *May*, 569
Digestive system, congenital anomalies, vomiting due to, *May*, 489
Dihydrostreptomycin, in brucellosis, *Feb.*, 82
  in tularemia, *Feb.*, 14
Disinfection in smallpox, *Feb.*, 26
Drugs, in obesity, *May*, 563
  parasympathomimetic, for constipation, *May*, 537
  vomiting due to, *May*, 501
Ductus arteriosus, patent, heart murmur in, *May*, 446
Duodenal fluid, analysis, as test of pancreatic function, *Feb.*, 202
    findings, *Feb.*, 205
Duodenum, obstruction, vomiting due to, *May*, 492
Dysmenorrhea, *May*, 545

Eczema vaccinatum, *Feb.*, 29
Edema, at infusion sites, *May*, 394
  in infancy, *May*, **391–402**
  in infants of diabetic mothers, *May*, 395
  nonpitting, *May*, 398
  of newborn infant, *May*, 339
  pitting, *May*, 391
Eisenmenger complex. See *Heart, abnormalities.*
Eiweiss milk, *May*, 362
Electroencephalography. See under *Brain.*
Electrolyte therapy. See *Fluid and electrolyte therapy.*

Emotional agents, amenorrhea due to, *May*, 543
Encephalitis, electroencephalogram in, *Feb.*, 294
meningeal, cerebrospinal fluid in, *Feb.*, 233
postvaccination, *Feb.*, 31
Endocarditis, Candida, *Feb.*, 157
Endocrine disturbances, excessive menstruation due to, *May*, 547
vomiting due to, *May*, 499
Endocrine function tests in pediatric practice, *Feb.*, **213–225**
Enema, cleansing, for constipation, *May*, 535
retention, for constipation, *May*, 536
Environment, weight gain failure due to, *May*, 570
Eosinophile count, stool, in milk allergy, *May*, 505
Ephedrine nose drops for allergic rhinitis, *May*, 423
Epiglottitis, acute, *May*, 380
Epilepsy, abdominal, vomiting due to, *May*, 498
electroencephalogram in, *Feb.*, 295
focal, electroencephalogram in, *Feb.*, 297
petit mal, electroencephalogram in, *Feb.*, 297
variant, electroencephalogram in, *Feb.*, 296
psychomotor seizures, *Feb.*, 300
temporal lobe foci, anterior, electroencephalogram in, *Feb.*, 300
with 14- and 6-per-second spikes, electroencephalogram in, *Feb.*, 299
Epileptic focus, midtemporal, electroencephalogram in, *Feb.*, 299
Epstein's pearls, *May*, 342
Erythema, toxic, of newborn, *May*, 338
Erythroblastosis fetalis. See *Hemolytic disease of newborn.*
Erythrocyte, abnormalities, as indication for bone marrow examination, *Feb.*, 253
sedimentation rate in brucellosis, *Feb.*, 81
Esophagus, atresia, vomiting due to, *May*, 489
diverticulum, vomiting due to, *May*, 490
Ethyl vannillate in histoplasmosis, *Feb.*, 144
Examination of newborn infant, *May*, **335–349**
Exanthem subitum. See *Roseola infantum.*
Extremities in newborn infant, *May*, 346
Eye(s), abnormalities, headache due to, *May*, 599
in newborn infant, *May*, 342

Face in newborn infant, *May*, 342
Fainting. See *Syncope.*
Fainting child, *May*, **605–613**
Fallot, tetralogy of. See under *Heart, abnormalities.*
Familial autonomic dysfunction, vomiting due to, *May*, 501
Fat(s), necrosis, subcutaneous, *May*, 339
requirements in artificial infant feeding, *May*, 355
Fat child, *May*, **553–565.** See also *Obesity.*
Fatigue, headache due to, *May*, 599
irritability and headache, *May*, **595–603.** See also *Headache.*
Feces, bilirubin, as test of liver function, *Feb.*, 180
blood in, *May*, **513–525**
with diarrhea, *May*, 519
eosinophile count in milk allergy, *May*, 505
examination as test of pancreatic function, *Feb.*, 207
in newborn infant, *May*, 348
tarry, *May*, 523
Feeding, infant, artificial, appraisal, *May*, **351–372**
chemical principles, *May*, 354
controversial concepts, *May*, 370
dietary supplements, *May*, 365
earlier endeavors, *May*, 352
historical setting, *May*, 352
nutritional requirements, basic, *May*, 355
physiologic principles, *May*, 354
recent achievements, *May*, 352
therapeutic adjuncts, *May*, 365
types, *May*, 354
methods, vomiting due to, *May*, 488
relationship to vomiting, *May*, 485, 486
Fever, headache due to, *May*, 598
in coccidioidomycosis, *Feb.*, 114
unexplained, sudden, *May*, 381
Fibrinogen, blood, *Feb.*, 272
Fibrinoid diseases, blood protein changes in, *Feb.*, 271
Flocculation tests of liver function, *Feb.*, 181
falsely positive, *Feb.*, 188
Fluid and electrolyte therapy, *Feb.*, **317–326**
application, *Feb.*, 324
fluids used in, *Feb.*, 323
general principles, *Feb.*, 321
solutions for, *Feb.*, 322
Flush method of blood pressure measurements, *Feb.*, 260
Fontanels in newborn, *May*, 341
Food, composition of, vomiting due to, *May*, 488
Friction rub. See under *Heart.*
Fruit loaf in constipation, *May*, 534

Galactosemia, jaundice due to, *May*, 462
Gamma globulin. See *Globulin.*
Gastric. See *Stomach.*
Gelatin absorption test of pancreatic function, *Feb.*, 208

Gemonil in epilepsy, *May*, 608
Geniculate zoster. See *Ramsay Hunt syndrome.*
Genital canal, stenosis, congenital, dysmenorrhea due to, *May*, 545
Genitals, in newborn infant, *May*, 345
internal, infections of, dysmenorrhea due to, *May*, 546
organic disease of, excessive menstruation due to, *May*, 548
Globulin, gamma, *Feb.*, 273
in eczema vaccinatum, *Feb.*, 29
in progressive vaccinia, *Feb.*, 31
in smallpox, *Feb.*, 26
Glomerulonephritis. See *Nephritis, glomerular.*
Glottis, lesions, *May*, 405
Glucose in leptospirosis, *Feb.*, 98
Glucose tolerance test of pituitary function, *Feb.*, 214
Glycerin suppository for constipation, *May*, 535
Gonadotropin excretion as test of pituitary function, *Feb.*, 214
Gonads, tests of function, *Feb.*, 222
Granulocytopenia as indication for bone marrow examination, *Feb.*, 252
Granuloma, coccidioidal. See *Coccidioidomycosis.*
Granuloma pyogenicum, *May*, 619
Growth hormone production as test of pituitary function, *Feb.*, 215
Gynecomastia. See *Breast, hypertrophy, in male.*

HEAD in newborn infant, *May*, 340
Headache, age distribution, table, *May*, 597
diagnosis, *May*, 597
etiology, *May*, 595
in coccidioidomycosis, *Feb.*, 114
incidence, *May*, 596
irritability and fatigue, *May*, **595–603**
location, table, *May*, 598
post-traumatic, *May*, 600
treatment, *May*, 600
Heart, abnormalities, Eisenmenger complex, murmur in, *May*, 447
tetralogy of Fallot, murmur in, *May*, 447
disease, syncope due to, *May*, 609
failure, blood protein changes in, *Feb.*, 269
edema due to, *May*, 394
friction rub, *May*, 446
in newborn infant, *May*, 344
murmurs, *May*, 442
characteristics, *May*, 442
congenital cardiac and great vessel malformations, *May*, 446
diastolic, aortic, *May*, 445
evaluation, *May*, 443
functional, *May*, 444
interpretation, *May*, **441–448**
mid-diastolic, apical, *May*, 445
organic, acquired, *May*, 444
Heart, murmurs, physiologic or innocent, *May*, 444
presystolic, apical, *May*, 445
pulmonic, *May*, 445
systolic, apical blowing, *May*, 444
tricuspid, *May*, 445
sounds, *May*, 441
Hemangioendothelioma. See *Tumors, angioendothelioma.*
Hemangioma. See *Tumors, angioma.*
Hemangiosarcoma, *May*, 621
Hematoma, subdural. See *Meninges, hemorrhage.*
Hemoglobin abnormalities as indication for bone marrow examination, *Feb.*, 253
Hemolytic disease of newborn, *May*, 432
due to ABO incompatibility, *May*, 454
due to Rh incompatibility, *May*, 452
due to other blood group incompatibilities, *May*, 455
edema due to, *May*, 395
inspissated bile due to, *May*, 458
liver function tests in, *Feb.*, 184
Heparinoid substances, circulating, increase in, excessive menstruation due to, *May*, 549
Hepatitis, acute, liver function tests in, *Feb.*, 186
neonatal, *May*, 459
vomiting due to, *May*, 497
Heredity, weight gain failure due to, *May*, 570
Hernia, diaphragmatic, vomiting due to, *May*, 490
Histoplasmosis, *Feb.*, **127–149**
clinical manifestations, *Feb.*, 136
diagnosis, *Feb.*, 143
laboratory diagnosis, *Feb.*, 141
treatment, *Feb.*, 144
Hormone(s), administration, edema due to, *May*, 395
growth, production of, as test of pituitary function, *Feb.*, 215
Hydrophobia. See *Rabies.*
Hyperglobulinemia. See *Hyperproteinemia.*
Hyperproteinemia, *Feb.*, 270
and hypoproteinemia, *Feb.*, 271
Hypersplenism. See *Splenomegaly.*
Hypoalbuminemia. See *Hypoproteinemia.*
Hypogammaglobulinemia, *Feb.*, 274
edema due to, *May*, 393
Hypoglycemia. See under *Blood sugar.*
Hypophysis. See *Pituitary body.*
Hypoproteinemia, *Feb.*, 268
and hyperproteinemia, *Feb.*, 271
edema due to, *May*, 392
in infancy, causes, table, *May*, 392
Hyposuprarenalism. See *Addison's disease.*
Hypothalamus, lesions, breast enlargement due to, *May*, 580
Hypothyroidism. See *Thyroid, hypothyroidism.*

Hypsarhythmia, electroencephalogram in, *Feb.*, 295

Ice, dry, for nevus vasculosus, *May*, 622
Icterus. See *Jaundice*.
Ileus, meconium, vomiting due to, *May*, 494
Illness, sudden, in infancy, *May*, **373–390**
Infant feeding. See under *Feeding*.
Infection(s), acute, vomiting due to, *May*, 489
chronic, blood protein changes in, *Feb.*, 271
enteral, vomiting due to, *May*, 496
headache due to, *May*, 598
in newborn, jaundice due to, *May*, 456
laryngeal edema due to, *May*, 407
parenteral, vomiting due to, *May*, 496
Pasteurella, *Feb.*, **3–17**
respiratory. See *Respiratory tract, infection*.
unusual, of childhood, symposium on, *Feb.*, **1–174**
weight gain failure in children due to, *May*, 571
weight gain failure in infancy due to, *May*, 569
Inheritance. See *Heredity*.
Inspection, general, of newborn infant, *May*, 337
Insulin tolerance test of pituitary function, *Feb.*, 214
Intestines, diverticula, Meckel's, rectal bleeding due to, *May*, 515
vomiting due to, *May*, 497
obstruction, functional, vomiting due to, *May*, 493
vomiting due to, *May*, 497
polyps, rectal bleeding due to, *May*, 517
Intracranial conditions, vomiting in newborn due to, *May*, 488
vomiting after neonatal period due to, *May*, 498
Intussusception, rectal bleeding due to, *May*, 516
vomiting due to, *May*, 497
Iodine level, protein-bound, as test of thyroid function, *Feb.*, 216
Iodine uptake, radioactive, as test of thyroid function, *Feb.*, 216
Iron, requirements, daily, table, *May*, 434
Iron deficiency anemia. See under *Anemia*.
Irritability, fatigue and headache, *May*, **595–603**. See also *Headache*.
Isolation in smallpox, *Feb.*, 26

Jaundice, after first week, *May*, 456
causes, table, *May*, 456
in first week, *May*, 450
causes, table, *May*, 449
in infancy, *May*, **449–464**
nonhemolytic, familial, congenital, with kernicterus, *May*, 462
Jaundice, obstructive, liver function tests in, *Feb.*, 185
prolonged, in infancy, differential diagnosis, *May*, 461
physiologic, in full term infant, *May*, 450
in premature infant, *May*, 450
of newborn, *May*, 338
prolonged, *May*, 461

Kernicterus, congenital familial nonhemolytic jaundice with, *May*, 462
Ketosteroid excretion as test of adrenal cortical function, *Feb.*, 221
Kidney, anomalies, congenital, function tests in, *Feb.*, 195
diseases, blood protein changes in, *Feb.*, 269
failure, acute, function tests in, *Feb.*, 197
functions, discrete, measurement of, *Feb.*, 191
impaired, edema due to, *May*, 392
tests, *Feb.*, **191–200**
clearance of endogenous substances, *Feb.*, 192
concentration of substances in blood, *Feb.*, 194
excretion of injected substances, *Feb.*, 193
in common kidney diseases, *Feb.*, 195
maximum concentrating capacity, *Feb.*, 195
procedures and methods, *Feb.*, 198
procedures and methods, *Feb.*, 197
Klinefelter's syndrome, gynecomastia due to, *May*, 590

Laboratory tests and special procedures, symposium on, *Feb.*, **175–326**
Laryngismus stridulus, *May*, 408
Laryngomalacia. See *Stridor, laryngeal*.
Laryngotracheobronchitis, *May*, 379
Larynx, congenital web, *May*, 406
cysts, *May*, 404
edema, *May*, 407
neoplasm, *May*, 408
Leptospirosis, *Feb.*, **87–100**
clinical picture, *Feb.*, 90
diagnosis, problem of, *Feb.*, 91
differential diagnosis, *Feb.*, 94
laboratory studies, *Feb.*, 92
treatment, *Feb.*, 95
Leukemia, *May*, 435
acute, as indication for bone marrow examination, *Feb.*, 247
bone marrow examination in, value, *Feb.*, 254
chronic, as indication for bone marrow examination, *Feb.*, 248
Leukemoid reactions as indication for bone marrow examination, *Feb.*, 251
Limping, *May*, 388

Lipoprotein metabolic disorders as indications for bone marrow examination, *Feb.*, 250
Liver, cirrhosis, breast enlargement due to, *May*, 591
function tests in, *Feb.*, 186
function tests, *Feb.*, **177–190**
clinical application, *Feb.*, 182
methods, *Feb.*, 179
normal values, *Feb.*, 179
granulomas of, function tests in, *Feb.*, 188
tumors, function tests in, *Feb.*, 188
Living, regimen of, weight gain failure due to, *May*, 571
Lumbar puncture. See *Spinal puncture.*
Lungs of newborn infant, *May*, 344
Lupus erythematosus, systemic, as indication for bone marrow examination, *Feb.*, 254
Lymphangioma. See *Tumors, angioma.*
Lyssa. See *Rabies.*

MALAISE in coccidioidomycosis, *Feb.*, 114
Malnutrition, blood protein changes in, *Feb.*, 268
Malta fever. See *Brucellosis.*
Mammoplasia, *May*, 586
Marrow, bone. See under *Bone.*
Massage, abdominal, for constipation, *May*, 536
Mecholyl for constipation, *May*, 537
Meckel's diverticulum. See *Intestines, diverticula.*
Meconium ileus, vomiting due to, *May*, 494
Meconium plug, constipation due to, *May*, 530
Medicated disk method of determining bacterial sensitivity to antibiotics, *Feb.*, 310
Mediterranean fever. See *Brucellosis.*
Meninges, hemorrhage, subdural hematoma, electroencephalogram in, *Feb.*, 294
Meningitis, *May*, 384
aseptic, allergic, *Feb.*, 53
Candida, *Feb.*, 157
coccidioidal, *Feb.*, 116
purulent, cerebrospinal fluid in, *Feb.*, 232
Meningitis syndrome, aseptic, acute. See *Aseptic meningitis syndrome, acute.*
Meningococcemia and acute adrenal insufficiency, *May*, 385
Menstrual problems of adolescent, *May*, **539–551**
causative factors, *May*, 539
differential diagnosis, *May*, 541
Menstruation, anovulatory, *May*, 546
excessive, *May*, 547
Mental deficiency, electroencephalogram in, *Feb.*, 302
Mesenteric adenitis, vomiting due to, *May*, 497
Metabolic disorders, lipoprotein, as indications for bone marrow examination, *Feb.*, 250
Migraine, headache due to, *May*, 598
Milk(s), acid, *May*, 364
albumin, *May*, 362
allergy to. See under *Allergy.*
classification, *May*, 358
composition, approximate percentage, table, *May*, 354
curd tension, *May*, 356
evaporated, *May*, 360
Eiweiss, *May*, 362
fresh, *May*, 357, 359
hypoallergenic, *May*, 363
premodified (one-formula), dried milks, *May*, 361
liquid milks, *May*, 362
proprietary, *May*, 357
protein, *May*, 362
protein supplements, *May*, 364
skimmed, *May*, 365
without added carbohydrate, *May*, 368
Milroy's disease, edema due to, *May*, 397
Minerals, excess intake, edema due to, *May*, 391
requirements, in artificial infant feeding, *May*, 355
Monilia infections. See *Candida infections.*
Mononucleosis, infectious, as indication for bone marrow examination, *Feb.*, 253
liver function tests in, *Feb.*, 188
Motion sickness, vomiting due to, *May*, 501
Mucous membranes, Candida infections, *Feb.*, 152
Mucus plug, constipation due to, *May*, 530
Mumps, nonglandular, vs. nonparalytic poliomyelitis, *Feb.*, 52
Murmurs, heart. See under *Heart.*
Mysoline in epilepsy, *May*, 607

NECK in newborn infant, *May*, 343
Neosynephrine nose drops for allergic rhinitis, *May*, 423
Nephritis, acute, kidney function tests in, *Feb.*, 196
glomerular, edema due to, *May*, 397
Nephrosis, kidney function tests in, *Feb.*, 197
Nephrotic syndrome, edema due to, *May*, 397
Nervous system, central, infections of, cerebrospinal fluid in, *Feb.*, 232
Neuromuscular status in newborn, evaluation, *May*, 347
Nevus, port wine, *May*, 615
spider, *May*, 619
Nevus araneus, *May*, 619
Nevus flammeus, *May*, 615
treatment, *May*, 621
Nevus vasculosus, *May*, 615
treatment, *May*, 622

Newborn infant, examination, *May*, **335–349**
Nitrogen, blood urea, as test of kidney function, *Feb.*, 194
nonprotein, as test of kidney function, *Feb.*, 194
Novatrin. See *Novatropine methylbromide.*
Novatropine methylbromide for constipation, *May*, 537
Nutritional factors, excessive menstruation due to, *May*, 548
Nuvarone in epilepsy, *May*, 608

OBESITY, clinical features, *May*, 557
etiologic factors, *May*, 554
management, *May*, 560
Obocell. See *Amphetamine phosphate.*
Ornithosis. See *Psittacosis.*
Oscillometry in blood pressure measurements, *Feb.*, 260
Osteoporosis, cranial, in newborn, *May*, 341
Otitis media, *May*, 383
Ovarian factors in amenorrhea, *May*, 541
Oxytetracycline in tularemia, *Feb.*, 15

PAIN, abdominal, vague, chronic, *May*, **465–481.** See also *Abdomen, pain in.*
pleural, in coccidioidomycosis, *Feb.*, 114
Pale child, *May*, **427–440**
Pallor, *May*, 427
Palpation method of blood pressure measurements, *Feb.*, 258
Palsy, cerebral. See *Cerebral palsy.*
Pancreas, annular, vomiting due to, *May*, 492
function tests, absorption tests, *Feb.*, 208
clinical response, *Feb.*, 209
direct, *Feb.*, 202
enzyme activity, *Feb.*, 203
exocrine, *Feb.*, **201–211**
indirect, *Feb.*, 207
PAR. See *Rhinitis, allergic, perennial.*
Paradione for convulsions, *May*, 611
Paralysis of vocal cords, *May*, 406
Parasitic disease, cerebrospinal fluid in, *Feb.*, 233
Parathyroids, function tests, *Feb.*, 224
Parenteral therapy. See *Fluid and electrolyte therapy.*
Pasteurella infections, *Feb.*, **3–17**
Pasteurelloses sensu strictu, *Feb.*, 15
Pearls, Epstein's, *May*, 342
Pelvis, congestion, dysmenorrhea due to, *May*, 547
Penicillin, in psittacosis, *Feb.*, 71
in smallpox complications, *Feb.*, 25
Peptic ulcer, vomiting due to, *May*, 497
Peritonitis, pelvic, dysmenorrhea due to, *May*, 546
vomiting due to, *May*, 497
Petit mal. See under *Epilepsy.*
Phenacemide. See *Phenylacetylurea.*
Phenobarbital in leptospirosis, *Feb.*, 98
Phenurone. See *Phenylacetylurea.*
Phenylacetylurea in epilepsy, *May*, 607
Phosphate level, serum, as test of pituitary function, *Feb.*, 215
Physical examination of newborn infant, *May*, 336
Pituitary body, anterior lobe, tests of function, *Feb.*, 214
dysfunction, amenorrhea due to, *May*, 542
hypopituitarism, amenorrhea due to, *May*, 543
posterior lobe, tests of function, *Feb.*, 223
Plague, *Feb.*, 3–10
bubonic, *Feb.*, 6
clinical aspects, *Feb.*, 5
diagnosis, *Feb.*, 7
pneumonic, *Feb.*, 6
septic, *Feb.*, 6
treatment, *Feb.*, 8
Pneumonia, *May*, 383
Pneumonitis, interstitial or viral. See *Bronchiolitis.*
Poisoning, chronic, blood protein changes in, *Feb.*, 269
Poliomyelitis, 1955, *May*, **629–638**
nonparalytic, vs. nonglandular mumps, *Feb.*, 52
Polyostotic fibrous dysplasia, breast enlargement due to, *May*, 582
Polyps, intestinal, rectal bleeding due to, *May*, 517
Posture in newborn infant, *May*, 337
Postvaccination encephalitis, *Feb.*, 31
Potassium, and sodium exchange, intracellular, edema due to, *May*, 394
concentration, as test of adrenal cortical function, *Feb.*, 219
Pregnancy, amenorrhea due to, *May*, 541
Premature infant, *May*, 348
jaundice in, *May*, 450
Privine nose drops for allergic rhinitis, *May*, 423
Prostigmin Bromide for constipation, *May*, 537
Protein(s), gastric digestion, importance of, *May*, 356
in cerebrospinal fluid, *Feb.*, 230
loss, *Feb.*, 269
requirements, in artificial infant feeding, *May*, 355
Pseudotuberculosis, *Feb.*, 15
Psittacosis, *Feb.*, 68–71
and Q fever, *Feb.*, **65–72**
laboratory diagnosis, *Feb.*, 70
treatment, *Feb.*, 71
Psychic factors, amenorrhea due to, *May*, 543
excessive menstruation due to, *May*, 548
Puberty, precocious, true, breast enlargement due to, *May*, 580
pseudoprecocious, breast enlargement due to, *May*, 584

Puberty, pseudoprecocious, medicational, breast enlargement due to, *May*, 587
Pulmonary valve, stenosis, heart murmur in, *May*, 447
Purpura, *May*, 385
  nonthrombocytopenic, *May*, 387
  thrombocytopenic, *May*, 386
Pyelonephritis, *May*, 382
Pylorospasm, vomiting due to, *May*, 491
Pylorus, stenosis, vomiting due to, *May*, 491
Pyrimethamine in toxoplasmosis, *Feb.*, 173

Q FEVER, *Feb.*, 65–68
  and psittacosis, *Feb.*, **65–72**
  laboratory diagnosis, *Feb.*, 67
  treatment, *Feb.*, 68
Query fever. See *Q fever*.

RABIES, *Feb.*, **55–63**
  clinical picture, *Feb.*, 59
  diagnosis, *Feb.*, 59
  treatment, *Feb.*, 61
Ramsay Hunt syndrome, *Feb.*, **41–45**
    differential diagnosis, *Feb.*, 43
    treatment, *Feb.*, **44**
Rash in coccidioidomycosis, *Feb.*, 114
Rat-bite fevers, *Feb.*, **101–108**
    clinical picture, *Feb.*, 104
    diagnosis, *Feb.*, 105
    differential features, *Feb.*, 105
    laboratory diagnosis, *Feb.*, 106
    treatment, *Feb.*, 106
Rectum, bleeding from, neonatal, *May*, 521
    symptoms, table, *May*, 513
    syndromes, clinical entitites in, table, *May*, 514
  lesions, bleeding from, *May*, 522
  malformations, vomiting due to, *May*, 494
Regurgitation, habitual, *May*, 496. See also *Vomiting*.
Respiratory stridor, infant with, *May*, **403–411**
Respiratory tract, Candida infections, *Feb.*, 156
    upper, allergic and infectious conditions, differential diagnosis, table, *May*, 416
    infections, recurrent, *May*, 413
      complications, *May*, 420
      diagnosis, *May*, 416
      differential diagnosis, *May*, 414
      incidence, *May*, 413
      treatment, *May*, 420
Retention enema for constipation, *May*, 536
Reticuloendothelial system, diseases involving, blood protein changes in, *Feb.*, 270
Rh factor. See under *Blood, groups*.
Rhinitis, allergic, perennial, *May*, 417
      complications, *May*, 420
      symptoms, *May*, 418
      treatment, *May*, 420
Riley-Day syndrome. See *Familial autonomic dysfunction*.
Roentgenograms in coccidioidomycosis, *Feb.*, 120
Roentgenographic indications for tracheography and bronchography, *Feb.*, 280
Roseola infantum, *May*, 381
Rumination, *May*, 496. See also *Vomiting*.
RURI. See under *Respiratory tract, upper, infections, recurrent*.

SAJODIN test of pancreatic function, *Feb.*, 207
San Joaquin Valley disease. See *Coccidioidomycosis*.
Sepsis, *May*, 384
Serum. See under *Blood*.
Sickle cell anemia as indication for bone marrow examination, *Feb.*, 253
Sinusitis, headache due to, *May*, 600
Skeleton. See *Bones*.
Skin, Candida infections, *Feb.*, 153
  of newborn infant, *May*, 338
Skin test, coccidioidin, *Feb.*, 116
    for cat scratch disease, *Feb.*, 37
    histoplasmin, *Feb.*, 142
Smallpox, *Feb.*, 19–27
  and vaccinia, *Feb.*, **19–32**
  clinical picture, *Feb.*, 21
  differential diagnosis, *Feb.*, 23
  hemorrhagic, *Feb.*, 23
  laboratory diagnosis, *Feb.*, 24
  treatment, *Feb.*, 25
  vaccination. See under *Vaccination*.
  variola minor, *Feb.*, 23
Soap suppository for constipation, *May*, 535
Sodium concentration as test of adrenal cortical function, *Feb.*, 219
Sounds, heart, *May*, 441
Space-occupying lesions, cerebrospinal fluid in, *Feb.*, 236
Spasm, cardioesophageal. See *Achalasia*.
Spherocytosis, congenital. See *Anemia, hemolytic, familial, congenital*.
Spider nevus, *May*, 619
Spinal puncture, lumbar, *Feb.*, 229
Splenomegaly as indication for bone marrow examination, *Feb.*, 254
Sputum examination in plague, *Feb.*, 8
Stomach, duplication, vomiting due to, *May*, 491
  irritation, vomiting due to, *May*, 488
Stools. See *Feces*.
Strawberry mark, *May*, 615
Streptomycin, in plague, *Feb.*, 9
  in tularemia, *Feb.*, 14
Stridor, as indication for tracheography and bronchography, *Feb.*, 280
  expiratory, *May*, 409
  inspiratory, *May*, 404

Stridor, laryngeal, congenital, *May*, 405
respiratory, infant with, *May*, **403–411**
Subdural hematoma, electroencephalogram in, *Feb.*, 294
Subdural taps, *Feb.*, **239–242**
equipment for, *Feb.*, 240
technique, *Feb.*, 240
Subglottic lesions, *May*, 408
Subglottic stenosis, congenital, *May*, 408
Sucking callus, *May*, 342
Sugar, additives, review, *May*, 367
in cerebrospinal fluid, *Feb.*, 230
Sulfadiazine, in brucellosis, *Feb.*, 82
in toxoplasmosis, *Feb.*, 173
Sulfonamide, triple, in brucellosis, *Feb.*, 82
Suppository, soap or glycerin, for constipation, *May*, 535
Supraglottic lesions, *May*, 404
Supraglottic web, *May*, 405
Sweats, night, in coccidioidomycosis, *Feb.*, 114
Swineherd's disease. See *Leptospirosis*.
Symptoms, presenting, diagnosis by, symposium on, *May*, **333–627**
Syncope, *May*, 605
carotid sinus, *May*, 608
Systemic diseases, cerebrospinal fluid in, *Feb.*, 236
amenorrhea due to, *May*, 543

TEMPER tantrums, syncope due to, *May*, 606
Tension, headache due to, *May*, 599
Terramycin. See *Oxytetracycline*.
Testis, tumors, breast enlargement due to, *May*, 589
Tetracyclines in smallpox complications, *Feb.*, 25
Tetralogy of Fallot. See under *Heart, abnormalities*.
Thalassemia, *May*, 438
Thin child, *May*, **567–573**. See also *Body weight, gain in, failure of*.
Thorax in newborn infant, *May*, 343
Thorium-X in nevus flammeus, *May*, 621, 622
Throat, sore, in coccidioidomycosis, *Feb.*, 114
Thrush, *Feb.*, 152
Thymol flocculation test of liver function, *Feb.*, 181
Thyroglossal duct cyst, *May*, 404
Thyroid, disease, breast enlargement due to, *May*, 592
weight gain failure in children due to, *May*, 571
weight gain failure in infants due to, *May*, 570
function tests, *Feb.*, 216
hypothyroidism, amenorrhea due to, *May*, 543
medication as test of thyroid function, *Feb.*, 218
Toxocara infections. See *Visceral larva migrans*.
Toxoplasmosis, congenital and acquired, *Feb.*, **169–174**
laboratory studies, *Feb.*, 172
treatment, *Feb.*, 173
Trachea, compression with vascular anomalies, *May*, 410
cyst, congenital, *May*, 410
lesions, *May*, 409
stenosis, congenital, *May*, 409
Tracheogram, equipment for, *Feb.*, 282
procedure, *Feb.*, 283
Tracheography and bronchography, *Feb.*, **279–289**
anesthesia for, *Feb.*, 281
contraindications, *Feb.*, 281
indications, *Feb.*, 279
postoperative care, *Feb.*, 287
preoperative preparation, *Feb.*, 281
technique, *Feb.*, 282
Tracheomalacia, *May*, 409
Trauma, laryngeal edema due to, *May*, 407
psychic, dysmenorrhea due to, *May*, 547
Tricuspid valve, atresia, heart murmur in, *May*, 447
Tridione in convulsions, *May*, 610
Tube-dilution method of determining bacterial sensitivity to antibiotics, *Feb.*, 310
Tube-to-plate method of determining bacterial sensitivity to antibiotics, *Feb.*, 310
Tuberculosis, meningeal, cerebrospinal fluid in, *Feb.*, 233
Tularemia, *Feb.*, 10–15
abdominal type, *Feb.*, 13
clinical characteristics, *Feb.*, 12
cutanoglandular type, *Feb.*, 12
generalized, *Feb.*, 13
laboratory diagnosis, *Feb.*, 13
oculoglandular type, *Feb.*, 12
oral glandular type, *Feb.*, 13
thoracic type, *Feb.*, 13
treatment, *Feb.*, 14
Tumors, angioendothelioma, *May*, 621
angioma, hemangioma, *May*, **615–624**
cavernous, *May*, 615
treatment, *May*, 623
cycle, *May*, 616
development, *May*, 615
differential diagnosis, *May*, 619
pathology, *May*, 616
subglottic, *May*, 408
treatment, *May*, 621
lymphangioma, *May*, 620
subglottic, *May*, 408
angioma serpiginosum, *May*, 620
breast enlargement due to, *May*, 592

UNDULANT fever. See *Brucellosis*.
Urea clearance test of kidney function, *Feb.*, 192
procedures and methods, *Feb.*, 197

Urea nitrogen, blood, as test of kidney function, *Feb.*, 194
Urinary tract, anomalies, vomiting due to, *May*, 498
Candida infections, *Feb.*, 157
Urine, bilirubin, test of liver function, *Feb.*, 179
examination for protein and blood cells, *Feb.*, 195
in newborn infant, *May*, 347
urobilinogen, test of liver function, *Feb.*, 179
Urobilinogen, urine, as test of liver function, *Feb.*, 179
Uterus, hypoplasia, dysmenorrhea due to, *May*, 545

VACCINATION, smallpox, *Feb.*, 26
complications, *Feb.*, 29
early or immediate reaction, *Feb.*, 28
vaccinoid reaction, *Feb.*, 28
Vaccinia, *Feb.*, 27–31
and smallpox, *Feb.*, **19–32**
generalized, *Feb.*, 30
progressive, *Feb.*, 30
prolonged, *Feb.*, 30
Vaccinia necrosum, *Feb.*, 30
Valley fever. See *Coccidioidomycosis*.
Variola. See *Smallpox*.
Ventricular septum, defect of, heart murmur in, *May*, 447
Visceral larva migrans, diagnosis, *Feb.*, 166
due to infection with dog and cat ascarids, *Feb.*, **163–168**
symptoms and signs, *Feb.*, 165
treatment, *Feb.*, 167
Vision, acuity, determination, *May*, 626
technique, *May*, 627
Vitamin(s), requirements in artificial infant feeding, *May*, 355
Vitamin A absorption test of pancreatic function, *Feb.*, 208
Vitamin K in leptospirosis complications, *Feb.*, 98
Vocal cord paralysis, *May*, 406
Volvulus, vomiting due to, *May*, 493
Vomiting, after neonatal period, *May*, 495
allergic, *May*, 500
colic and diarrhea due to milk allergy, *May*, **503–511**. See also *Allergy, milk*.
cyclic, *May*, 499
duration, *May*, 485
epidemic, *May*, 499
etiology, *May*, **483–502**
force of, *May*, 485
frequency, *May*, 485
history to determine causes, *May*, 486
in newborn infant, *May*, 487
laboratory data, *May*, 487
physical examination for, *May*, 487
psychogenic, *May*, 500
recurrent, *May*, 499
reflex, *May*, 501
relationship to feedings, *May*, 485, 486
roentgenographic studies, *May*, 487
Vomitus, character, *May*, 484

WATER, requirements, in artificial infant feeding, *May*, 355
Weight. See *Body weight*.
Weil's disease. See *Leptospirosis*.
Wheezing as indication for tracheography and bronchography, *Feb.*, 280

ZEPHIRAN chloride in bite wounds, *Feb.*, 61
Zoster, geniculate. See *Ramsay Hunt syndrome*.